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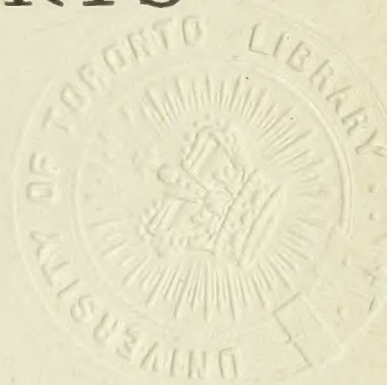### SERIES B—No. 1

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NITROGEN METABOLISM IN PERNICIOUS ANÆMIA BEFORE AND AFTER SPLENECTOMY

By E. H. Mason and J. Kaufmann.

(*From the medical service of Professor Charles F. Martin*)

THIS report embodies the studies made upon the nitrogen metabolism of a case of pernicious anæmia that was recently admitted to the wards of the Royal Victoria Hospital. The case was a typical one of pernicious anæmia on whom various methods of treatment were tried over extended periods of time with the usual temporarily favorable results.

The investigation consisted of a study of the nitrogen balance during two periods, one two weeks previous to splenectomy of six days duration, but, unfortunately, owing to an error in the collection of the stools, our balance sheet shows only a five-day period; the other one month after splenectomy of five days duration. During the first period the patient was placed upon a constant diet containing 10 grm. of nitrogen per day, it being possible to maintain the intake exactly the same throughout, but during the second period, to satisfy the patient, it was found necessary to increase the intake to an average of 13.9 grm. of nitrogen per day. The diet in both periods was started three days before saving specimens for analysis.

A daily nitrogen partition of the urine, as well as an estimation of the total nitrogen, urea, and ammonia in the stools were made during both periods.

Methods Employed

The values of the diets were figured from Atwater and Bryant's[1] food analysis tables. The food stuffs were not analysed. The urine was collected from 7 A.M. to 7 A.M. under toluol and a complete analysis was made each day.

The stools were sent to the laboratory immediately upon collection and kept acidified with $\frac{n}{10}$ sulphuric acid to avoid loss of ammonia and conversion of urea. They were then evaporated to dryness upon a water bath, further dried in a dessicator over calcium chloride, and pulverized. Every morning at 6 A. M. the patient received an enema of physiological saline which completed the stool collection for the previous day.

METHODS

Total Nitrogen: By Kjeldahl-Gunning method.

Urea, Urea-nitrogen: Van Slyke and Cullen's[2] modification of Marshall's[3] urease method.

Ammonia, Ammonia-nitrogen: Folin's micro-method[4].

Creatinine, Creatinine-nitrogen: Folin's original method[5], using $\frac{n}{2}$ Potassium Bichromate standard.

Creatine, Creatine-nitrogen: Folin's original method[6].

Uric acid, Uric acid-nitrogen: S. Benedict's colorimetric method[7].

SUMMARY OF CASE

Case No. 23384. T. J., white, age 35. A farmer by trade. Born in Canada. Admitted to R. V. H. Nov. 23, 1915, complaining of shortness of breath and weakness on slight exertion.

Present Illness: Onset of illness was in the summer of 1914 with marked weakness, which increased gradually so that in December 1914 he was forced to give up his usual work, but was able to attend to minor duties until April 1915. At that time he had a relapse, which lasted a short while, but in May of the same year he again felt improved. He had another relapse in September 1915 and in October 1915, with both attacks suffering from marked shortness of breath.

Family History: Good.

Personal History: Good.

Present Condition: Poorly nourished anæmic man with lemon tinge to skin. Subcutaneous fat plentiful and slight œdema about both ankles. Respiratory system is normal.

Cardio-vascular system: Pulse rate 82. Blood pressure: systolic 108, diastolic 54. Heart: The transverse diameter is 15 cm. and the usual "anæmic" murmur is to be heard over the præcordium. Gastro-intestinal system: The gums show a slight pyorrhœa alveolaris. The liver is just palpable and slightly larger than normal. The spleen is large, firm, and easily palpated, extending 2.5 cm. below the costal margin, but it is not tender.

The nervous system is normal.

Save for occasional hyaline casts and a low sp. gr. of 1009 to 1010 the urine shows nothing of importance. Stools: normal. There are no ova, parasites, or blood. Blood on admission shows R.B.C. of 1,460,000, W.B.C. 3,400, and Hb 27% (Sahli). There is slight poikilocytosis with a few microcytes and macrocytes. Fundi are pale and there are marked myopic crescents in both eyes. Cerebro-spinal fluid is normal. Gastric analysis: 90 c.c. withdrawn at end of one hour. There is no free acid, with a combined acidity of 10. No blood or lactic acid. Microscopical examination shows nothing abnormal.

Differential Blood Count: 200 cells counted.

Neut.: 34.0 %. Eos.: 0.0 Bas. 0.5%. Small lymph.: 50.0%. Large lymph.: 14.0%. End. Leuk.: 1.5%.

After making a diagnosis patient left hospital in November 27, 1915, to return later for treatment. Accordingly he was readmitted in February 16, 1915, all his symptoms having become much worse. It was decided to perform a splenectomy, preceded and followed by transfusions of small quantities of blood. The first transfusion of 300 c.c. was given on March 4, 1916, after which he was transferred to surgery on March 8, 1916, and splenectomy was performed in March 10, 1916, the same day receiving a transfusion of 300 c.c. of blood. Another transfusion was given in March 20, 1916, of 450 c.c. of blood.

Upon operation the spleen was found to be considerably enlarged and two small accessory spleens were present, one the size of a plum and the other a little smaller. One of these accessory spleens was left. The pathological report follows:

"Large succulent spleen. Weighs 469 grm. Measurements: 17 x 10 x 5 cm. Edges rounded. Capsule slightly thickened. Cut surface: Malpighian corpuscles are plainly seen. Dark in colour. Microscopical examination: marked hæmolysis of R.B.C. within pulp and sinuses, there being excessive pigmentation throughout. The individual R.B.C. have largely disappeared, but are fused to a homogenous, œdematous and hyaline mass within the splenic pulp which appears extremely poor in pulp cells. This fusion is also present in blood vessels of sinuses and of Malpighian corpuscles."

The blood picture throughout his hospital stay follows:

Date	R.B.C.	W.B.C.	Hb (Sahli)	Colour Index
Feb. 17, '16	824,000	3,175	13%	0.8
Feb. 27, '16	980,000	3,000	15%	0.8
March 1, '16	992,000	3,000	20%	1.1
*March 6, '16	1,264,000	3,050	18%	0.7
March 9, '16	1,110,000	3,000	25%	1.2
March 10, '16	Splenectomy	......	......	......
March 20, '16	1,210,000	3,800	25%	1.2
March 28, '16	2,220,000	......	40%	0.9
April 2, '16	1,624,000	4,200	22%	0.9
April 21, '16	2,064,000	6,600	25%	0.6

*Many poikilocytes, macro- and microcytes. Anisocytosis. Diffuse and punctate polychromatophilia. A few megaloblasts. No normoblasts.

DIFFERENTIAL BLOOD COUNTS

Date	Cells Counted	Neut.	Eos.	Bas.	Small Lymph.	Large Lymph.	End. Leuk.
Nov. 24, '15	200	34.0	0.0	0.5	50.0	14.0	1.5
*Mar. 6, '16	200	45.0	2.5	0.0	34.0	5.0	5.0
Apr. 20, '16	200	86.9	0.0	0.0	4.0	5.3	3.8

*NOTE—Neutrophilic myelocytes 2. Megaloblasts 2.

Notes in Regard to Investigation

Before splenectomy: The patient was placed upon the special diet February 18, 1916, and the period during which the studies were made was from February 22 to 27 inclusive. The diet consisted the following values: Protein 62 grm.; Fat 86 grm.; CHO 262 grm.; which yielded 2139 calories. The diet was practically purin free. His temperature was normal throughout.

Splenectomy was done on March 10, 1916, it being uneventful. The studies were not renewed until one month later, when on April 12, 1916, he resumed his former diet, but as the diet seemed to be insufficient to satisfy his appetite extra food in the form of eggs and bread was given. Otherwise the diet was the same. The specimens for analysis were collected from April 14 to 18 inclusive. Throughout the period there was no fever and his weight remained constant.

After the conclusion of the studies he was discharged on April 21, 1916, in a greatly improved condition. After leaving the hospital he was around for about four weeks, then all the previous symptoms returned, confining him to his bed. His condition grew gradually worse and death occurred on August 9th, 1916.

NITROGEN METABOLISM BEFORE SPLENECTOMY

Date	Urine Amt. c.c.	Sp. Gr.	Total N Grm.	Urea Grm.	Urea N Grm.	Urea N % of Total N	NH_3 Grm.	NH_3N Grm.	NH_3N % of Total N
Feb. 22, '16	1,500	1,011	5.45	4.95	2.34	42.9	0.24	0.20	3.7
Feb. 23, '16	1,700	1,010	5.78	5.10	2.41	41.8	0.29	0.24	4.1
Feb. 24, '16	1,800	1,010	5.65	8.46	3.96	70.1	0.62	0.51	9.0
Feb. 25, '16	1,600	1,012	7.52	8.48	3.97	52.8	0.88	0.72	9.6
Feb. 26, '16	1,750	1,015	8.22	11.76	5.51	67.0	0.42	0.35	4.2
Feb. 27, '16	1,600	1,016	7.52	9.68	4.54	60.4	0.49	0.40	5.3
Average	1,658	1,012	6.69	8.07	3.79	55.8	0.49	0.40	5.9

Date	Creatinine Grm.	Creatinine N Grm.	Creatinine N % of Total N	Uric Acid Grm.	Uric Acid N Grm.	Uric Acid N % of Total N	Undetermined N Grm.	Undetermined N % of Total N
Feb. 22, '16	0.84	0.30	5.5	0.42	0.14	2.6	2.17	45.3
Feb. 23, '16	0.95	0.35	6.0	0.42	0.14	2.4	2.64	45.7
Feb. 24, '16	0.97	0.36	6.4	0.54	0.18	3.2	0.63	11.3
Feb. 25, '16	0.92	0.34	4.5	0.56	0.19	2.2	2.30	30.9
Feb. 26, '16	0.96	0.36	4.4	0.77	0.25	3.0	1.75	21.4
Feb. 27, '16	0.92	0.34	4.5	0 65	0.21	2.8	2.03	27.0
Average	0.93	0.34	5.2	0.56	0.18	2.7	1.92	30.3

NITROGEN METABOLISM AFTER SPLENECTOMY

Date	Urine Amt. c.c.	Sp. Gr.	Total N Grm.	Urea Grm.	Urea N Grm.	Urea N % of Total N	NH₃ Grm.	NH₃N Grm.	NH₃N % of Total N
April 14, '16	1,400	1,017	9.64	11.25	5.27	54.6	0.96	0.79	8.3
April 15, '16	1,600	1,016	9.76	10.69	4.86	49.8	1.41	1.16	12.0
April 16, '16	1,300	1,017	10.05	7.13	3.35	33.3	1.02	0.85	8.4
April 17, '16	1,500	1,019	10.24	15.60	7.29	71.2	1.12	0.93	9.0
April 18, '16	1,400	1,017	8.10	11.62	5.44	67.1	1.05	0.87	10.7
Average	1,440	1,017	9.55	11.26	5.24	55.2	1.11	0.92	9.7

Date	Creatinine Grm.	Creatinine N Grm.	Creatinine N % of Total N	Uric Acid Grm.	Uric Acid N Grm.	Uric Acid N % of Total N	Undetermined N Grm.	Undetermined N % of Total N
April 14, '16	0.70	0.26	2.7	0.64	0.20	2.0	3.11	32.4
April 15, '16	0.81	0.30	3.1	0.54	0.18	1.8	3.25	33.3
April 16, '16	0.63	0.24	2.3	0.47	0.15	1.4	5.46	54.6
April 17, '16	0.81	0.30	2.9	0.55	0.18	1.7	1.54	15.2
April 18, '16	0.56	0.20	2.4	0.54	0.18	2.2	1.41	17.6
Average	0.70	0.26	2.7	0.54	0.18	1.8	2.95	30.6

NITROGEN METABOLISM BEFORE SPLENECTOMY

Date	Faeces Weight Grm.	Total N Grm.	Urea Grm.	Urea N Grm.	Urea N % of Total N	NH_3	NH_3N Grm.	NH_3N % of Total N
Feb. 23, '16..	18.9	0.38	0.005	0.002	0.5	0.025	0.021	5.5
Feb. 24, '16..	24.4	1.36	0.007	0.003	0.2	0.066	0.054	3.9
Feb. 25, '16..	18.0	0.85	0.010	0.005	0.6	0.021	0.017	2.0
Feb. 26, '16..	23.8	1.06	0.000	0.000	0.0	0.131	0.108	10.2
Feb. 27, '16..	32.4	1.51	0.039	0.018	1.2	0.104	0.084	5.6
Average...	23.5	1.03	0.012	0.006	0.5	0.069	0.056	5.4

NITROGEN METABOLISM AFTER SPLENECTOMY

Date	Faeces Weight Grm.	Total N Grm.	Urea Grm.	Urea N Grm.	Urea N % of Total N	NH_3 Grm.	NH_3N Grm.	NH_3N % of Total N
April 14, '16..	45.0	2.45	0.121	0.056	2.3	0.068	0.056	2.3
April 15, '16..	23.9	1.34	0.025	0.011	0.9	0.016	0.013	0.8
April 16, '16..	38.8	1.93	0.161	0.075	3.9	0.026	0.021	1.0
April 17, '16..	11.6	0.62	0.062	0.028	4.5	0.005	0.004	0.6
April 18, '16..	57.6	3.30	0.172	0.080	2.4	0.264	0.218	6.6
Average...	35.4	1.93	0.108	0.050	2.8	0.076	0.062	2.2

BALANCE SHEET

BEFORE SPLENECTOMY

Date	Weight lbs.	Intake N. Grm.	Output N. Grm.			Balance Grm.
			Urine	Fæces	Total	
Feb. 23, '16.........	123.7	10.0	5.78	0.38	6.16	+3.84
Feb. 24, '16.........	123.2	10.0	5.65	1.36	7.01	+2.99
Feb. 25, '16.........	122.0	10.0	7.52	0.85	8.37	+1.63
Feb. 26, '16.........	121.2	10.0	8.22	1.06	9.28	+0.72
Feb. 27, '16.........	120.7	10.0	7.52	1.51	9.03	+0.97
Average........	...	10.0	6.93	1.03	7.97	+2.03

AFTER SPLENECTOMY

Date	Weight lbs.	Intake N. Grm.	Output N. Grm.			Balance Grm.
			Urine	Fæces	Total	
April 14, '16.........	110.0	13.7	9.64	2.45	12.09	+1.61
April 15, '16.........	110.0	13.7	9.76	1.34	11.10	+2.60
April 16, '16.........	109.7	13.7	10.05	1.93	11.98	+1.72
April 17, '16.........	110.0	14.9	10.24	0.62	10.86	+4.04
April 18, '16.........	111.0	12.5	8.10	3.30	11.40	+1.10
Average........	.....	13.9	9.55	1.93	11.48	+2.21

DISCUSSION OF RESULTS

1.   The nitrogen balance: von Noorden[8] was the first to carefully study the nitrogen metabolism in pernicious anæmia, and he claims that most cases show a marked nitrogen retention, but his work has been criticized as having been conducted during periods of regeneration of the hæmatopœtic organs.   The findings of others, notably those of Rosenquist[9], show that the presence of either a retention or a loss of nitrogen depends mainly upon the relation of the period of study to the well known cyclic course that a case of pernicious

anæmia pursues.   The prevailing idea that the cause of exten-
sive blood destruction in pernicious anæmia is of toxic origin
has been brought under severe criticism of late, as Milne[10]
and Skornjakoff[11] have been able to produce the exact
picture of pernicious anæmia by repeated bleedings.   Skorn-
jakoff has proved that by alternately bleeding rabbits to the
point of severe anæmia and then letting them recover myeloid
foci could be developed in the spleen, and less frequently in
the liver, as well as a blood picture with large numbers of
normoblasts, red blood cells with granular basophilia, and
myelocytes.   If such is the case Milne claims that a simple
regeneration will explain the picture found in the blood organs
in both pernicious anæmia and in experimental anæmias.
This would indicate that the so-called "toxic" anæmias and
those of post-hæmorrhagic origin are of the same nature; the
difference being more a matter of degree.

In the severe anæmias caused by the bothriocephalus
latus and ankylostoma we know that we have a nitrogen loss,
but upon removal of the worms from the gut a retention takes
place.

The work of Umber[12] is one of the most convincing
that we possess.   He made observations upon a case of
Banti's Disease in a boy of 15 years with a spleen that weighed
1300 grm.   Before and after removal of the organ he found no
difference in the nitrogen partition in the urine.   However,
before splenectomy he found it very difficult to maintain
nitrogen equilibrium unless he allowed a very high nitrogen
intake.   After splenectomy nitrogen equilibrium was obtained
upon a much lower intake.

Our case shows a nitrogen retention before splenectomy
over a five-day period of 10.15 grm., the daily average being
2.03 grm.   After splenectomy, the retention still continues,
but at a slightly higher level, the daily average for the five-day
period being 2.21 grm.

Despite the increased intake of nitrogen in the second
period, the assimilation apparently was quite complete, as the
bulk of the fæces and its nitrogen content were only slightly

increased over that of the earlier period, this increase being partly explained by the higher nitrogen intake. The outstanding fact remains, nevertheless, that there was a definite nitrogen retention in both periods, it being slightly increased after splenectomy.

The Nitrogen Partition—The Urine

1. *Urea-nitrogen:* The results in our case show fairly constant findings both before and after splenectomy, namely averages of 55.8% and 55.2% of the total nitrogen in the form of urea-nitrogen. In some respects these findings agree with those of others. Von Noorden[8] finds that most cases of pernicious anæmia show a low percentage of urea-nitrogen, especially advanced cases with œdema. Podoa thinks that there is a drop in the percentage of urea-nitrogen in all cases of anæmia. Minot[13] found a low percentage of urea-nitrogen before splenectomy. an average of 54.3% as against 79.6% after splenectomy. He explains the decrease as probably due to deranged liver function. We offer no explanation of our findings.

2. *Ammonia-nitrogen:* In partial agreement with other investigations we find a marked increase in the percentage of ammonia-nitrogen after splenectomy, before splenectomy the results being within normal limits. These findings are of interest in relation to his apparent exhaustion of reserve alkali as shown by the Sellard's tolerance test. Starting with March 6, 1916, he was given daily increasing doses of soda bicarbonate, namely 4 grm., 10 grm., 15 grm., and 20 grm., all failing to produce any change in the hydrogen-ion concentration in the urine. We have found this to be of common occurrence in pernicious anæmia.

3. *Creatinine-nitrogen:* The results are hard to explain, as the patient was on a constant diet. Such fluctuations are unusual. The low percentage results of the second period are partly to be explained by the increased nitrogen intake in the form of creatinine free foods.

4. *Creatine-nitrogen:* The case excreted no creatine.

5. *Uric acid-nitrogen:* The low output of uric acid may be explained by the practically purin-free diet, that excreted being of endogenous nature. The actual amount excreted is constant in both periods, but in relation to the total nitrogen the percentage changes, proving its endogenous nature.

The quantities of uric acid excretion in pernicious anæmia has largely been elucidated by the demonstration of uricolytic ferments in most of the abdominal organs, so no longer can we lay that function exclusively to the spleen. Most investigators have found no change before and after splenectomy when on a purin-free diet, showing that the endogenous uric acid metabolism is not greatly influenced by the removal of the spleen (Umber,[12] Mendel and Gibson,[14] Paton.[15]) Recently Pepper and Austin[16] have published results showing a decrease in the uric acid excreted of 22% after splenectomy.

6. *The undetermined Nitrogen:* In our investigations the amino-acid nitrogen fraction of this undetermined nitrogen was not determined. Before splenectomy 30.3% of the total nitrogen, as against 30.6% of the total nitrogen after splenectomy, was in the form of undetermined nitrogen. The constancy of the finding is remarkable. However, the individual daily variations are extreme, ranging from 11.3% to 54.6%. The values vary inversely as the percentage of urea-nitrogen.

By some other investigators the amino-acid nitrogen has been found to be increased. However, most of the results were obtained by older methods which are not above criticism. Erben[17] in one case found it much increased. Samuely,[18] working with experimental anæmia, also reported similar results, but he thinks that the increase can be explained by other causes than the anæmia.

The fæces: The striking fact is their increased bulk in the second period, with a correspondingly higher nitrogen content which is proportional to the increased nitrogen intake.

Conclusions: Studies in a case of pernicious anæmia show a practically unchanged nitrogen metabolism both before and after splenectomy. In detail:

1. During both periods there is a practically unchanged nitrogen retention of 2.0 grm. per day.

2. The percentage of the urea-nitrogen of the total nitrogen remains unchanged at the low level of 55.8% and 55.2% respectively.

3. The percentage of ammonia-nitrogen increases slightly after splenectomy.

4. The uric acid-nitrogen excretion is constant during both periods.

5. The undetermined nitrogen remains constantly at the very high level of 30% of the total nitrogen in both periods. Daily the percentage varies inversely as the percentage of urea-nitrogen.

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THE NITROGEN PARTITION OF THE URINE IN TRINITROTOLUENE POISONING— A PRELIMINARY NOTE

By V. J. Harding and E. H. Mason

(From the medical service of Professor Charles F. Martin and the Clinical Laboratories)

Among the many problems presented by the war, the health of the munition workers is not one of the least important, and this applies in force to those exposed to the physiological action of the newer high explosives, manufactured in many cases under new and at first adverse conditions. In this connection the manufacture of trinitrotoluene (T.N.T. Triton. Trotyl., etc.) has presented new problems to the medical profession, and we are fortunate in having been able to study a limited number of cases of this class of poisoning. Through the kindness of Dr. Hirschberg of the Canadian Explosives Co. Ltd., and of Dr. Montpetit of Messrs. Curtis and Harvey (Canada) Ltd., we have been able to make a general study of the symptoms of trinitrotoluene poisoning. These have been dealt with in various orders issued by H.M. Government. designed to act as preventive measures against the poison, and although there are differences to be found, due, we believe, to the different conditions and modes of manufacture, nevertheless the general symptoms are in very close agreement.

Trinitrotoluene poisoning can take place through three channels—the first by absorption of the chemical through the skin during the daily handling of the material, the second by absorption through the gastro-intestinal tract, and the third by inhalation of the vapour or the dust of the shops. The early symptoms usually consist of a papular rash on an erythematous base of the exposed parts of the body, especially in the webs of the fingers. This papular eruption is very

itchy, is prone to infection with the usual pyogenic staphylo-cocci and streptococci of the skin, and will persist for a long time if the exposure continues. With the appearance of the rash there is usually experienced a sensation of general weak-ness which may become extreme. Anæmia rapidly appears, the hæmoglobin often dropping to 40%. Cyanosis of the lips is one of the early common symptoms. If the dust has been inhaled there is a marked tendency for hæmorrhages to take place from the nose, lungs, kidneys and intestines. Spectro-scopically the blood is negative. As the condition progresses jaundice usually appears, often of mild degree, but it may be severe. An enlarged spleen is not uncommon. These are the main symptoms of the condition, and their onset may appear a few days after exposure or may be long delayed.

Early in the condition there appears a deeply coloured urine, and as this change can become very marked it becomes of importance to study the nitrogen metabolism of such patients, the preliminary results of which are given here. We have examined the nitrogen partition in the urine of five case of T.N.T. poisoning taken at different stages of the disease.

CASE 1. Through the kindness of Dr. Lafleur this case was available for examination.

M. G.   Age 36.   Male.

After working for seven weeks in a T.N.T. plant he started to have an unproductive cough. Two days later jaundice appeared, which symptom gradually increased. With the inset of the jaundice there was irregular vomiting after meals, which lasted for three days.

On examination the findings were negative except for the jaundice and a decreasing absolute liver dulness. The spleen was never enlarged. The blood showed R.B.C. of 4,720,000; W.B.C. of 8,600, and Hb of 94%. The Wassermann reaction upon the blood was negative. The urine was dark in colour, acid, and contained a large amount of serum albumin with crystals of tyrosine, which persisted for the one month that the patient was under observation.

Case 2. An Indian. Age 23.

When seen was convalescent from jaundice. The conjunctivæ were still slightly icteroid, but the urine was practically free from bile.

Case 3. G. Student. Age 20.

Seen at the beginning of an attack of jaundice. Had previously been away from work because of dermatitis and cyanosis, but these symptoms had disappeared.

Case 4. A. S. Age 26. Service Dr. Martin. Case No. 24502.

Admitted to R.V.H. on September 4, 1916, complaining of general malaise with diffuse abdominal pain.

Personal History and Family History: Are both good.

Present Illness: After working for two months in T.N.T. plant began to vomit at irregular intervals. This continued until two weeks ago, when diffuse epigastric pain developed. Four days ago jaundice appeared. Since onset of vomiting he has felt very weak.

Present Condition: Skin and mucuous membrane are icteroid. Respiration and cardio-circulatory systems are normal.

Examination of abdomen shows an enlarged spleen, which is palpable two fingers' breadth below costal border. The edge is firm and rounded. The liver dullness extends from the fourth costal space to one finger's breadth above costal margin in the mid-clavicular line. There is no free fluid. Examination otherwise is normal.

Blood Pressure: Systolic 95. Diastolic 46.

Urine: Is of dark amber colour, acid in reaction, with a sp. gr. of 1018 to 1020. A trace of serum albumin is present, but sugar, bile and blood are absent. There are a few hyaline and granular casts.

Blood: R.B.C. 3,800,000. W.B.C. 15,000. Hb 58% (Sahli). Stools are normal.

Case 5. V. D. Age 39. Service Dr. Hamilton. Case No. 24399.

Admitted to R.V.H. on August 9, 1916, complaining of swelling of abdomen, dyspnœa, and pain in the lower back.

Personal History: Had malaria at nine years of age. Neisser infection at eighteen.

Family History: Good.

Present Illness: Started working in powder factory June 1, 1916, at which time he was quite well. About July 1, 1916, severe nose-bleeds began, always coming from the left nostril. These lasted for three weeks. At this time he was working in a room where he was breathing irritating fumes. Two weeks later he began to suffer from dragging pains in his left side, which gradually became worse, and his abdomen began to swell. Coincidently dyspnœa appeared.

Present Condition: Patient is a poorly nourished man with marked abdominal swelling. Mucous membranes are slightly jaundiced and there is considerable cyanosis of the lips. The lungs show a little passive congestion. The heart is normal. The abdomen is greatly distended with free fluid, but the spleen can be palpated by "dipping," the organ extending well below the costal margin. The liver is not palpable, and by percussion its upper border is at the level of the fourth intercostal space, the absolute dullness extending downwards five cm. in the mid-clavicular line. .

Blood Pressure: Systolic 100. Diastolic 60.

Blood: R.B.C. 3,840,000. W.B.C. 4,400. Hb 60% (Sahli).

Urine: Normal except for a trace of albumin and a few hyaline and granular casts.

In the Following Tables are Given the Nitrogen Partition in the Urine.
The Urine was Collected in Twenty-four Hour Periods.

Nitrogen Grm.	Case I		Case II		Case III		Case IV		Case V	
	In 24 Hours	Per cent of Total	In 24 Hours	Per cent of Total	In 24 Hours	Per cent of Total	In 24 Hours	Per cent of Total	In 24 Hours	Per cent of Total
Total.........	11.54	.....	12.56	.....	17.36	.....	11.76	.....	8.40	.....
Urea.........	8.72	75.60	6.46	51.4	12.73	73.3	4.72	40.1	3.34	39.7
Ammonia.....	0.59	5.34	0.74	5.9	1.10	6.3	0.66	5.6	1.36	16.2
Creatinine....	0.40	3.46	0.15	1.2	0.31	1.8	0.44	3.7	0.36	4.3
Creatine......	0.08	0.70	0.26	2.0	0.39	2.2	0.03	0.2	0.06	0.6
Uric Acid.....	0.27	2.34	0.34	2.6	0.43	2.4	0.21	1.8	0.11	1.3
Undetermined.....	1.47	12.73	4.63	36.9	2.40	13.9	5.69	48.4	3.17	37.7

An examination of the figures clearly shows that a big alteration is brought about in the nitrogen partition. The undetermined nitrogen in all cases is high, in three of them is excessively high, and it is the intention of the authors to pursue this subject further, extending the partition of the nitrogen still further, and examining a larger number of cases under controlled conditions of diet.

OBSERVATIONS ON THE ROTH MODIFICATION OF THE PLESCH METHOD OF ESTIMATING THE CARBON DIOXIDE TENSION OF THE ALVEOLAR AIR AS AN INDEX OF ACIDOSIS

By Maude E. Abbott

(*From the medical service of Professor C. F. Martin and the Clinical Laboratories*)

Among the many advances which have taken place in physiological knowledge in very recent times, none has had a more important or direct bearing upon the practical issues of clinical medicine than that which has established the specific chemical reaction of the blood as what may be termed a definite physiological constant, the variations in which imply corresponding degrees of disordered tissue metabolism, and the graver deviations, cellular and somatic death. In this sense, the maintenance of the hydrogen-ion concentration or acid-base equilibrium of the blood and tissues at the normal level of very slight alkalinity, with fluctuations within very narrow physiological limits, has been aptly likened to the range of the body temperature, and supplies a similar index of metabolic efficiency.

Until quite recently the exact determination of the blood and tissue reactions has been a complicated procedure beyond the scope of ordinary clinical application. But the rapid increase, during the last decade, of a knowledge of the factors that enter into its adjustment, and of metabolism in general, has yielded to-day a number of tests of quite easy application. These tests are based upon the now well known facts that the normal processes of metabolism are associated with extensive production of carbon dioxide and other organic acids, which are being constantly received into the blood

stream where they are as quickly neutralized by the various basic substances, carbonates, phosphates or proteins, held in weak solution there, and that conversely the disturbance in the normal proportions of any of these substances in the blood and tissues leads to an alteration of the acid-base equilibrium of the blood of the nature of a diminished alkalinity, recognized clinically under the term acidosis. The possible causes of such a disturbance are one with the factors that may enter into the adjustment of this equilibrium and may be enumerated as abnormal retention or over-production of acids, imperfect oxygenation and incomplete combustion of acid products, and diminished intake, or lessened formation, or excessive excretion of bases. In each case the result is the same—a pathological state of the body fluids incompatible with the proper functioning of enzyme reactions and those other delicate processes, the sum of which constitutes life.

Of all the evidences of acidosis, or more correctly of hypoalkalinity of the blood, the most constant is that yielded by the determination of its carbon dioxide content which is known to vary in inverse ratio with the organic acids present. This important point has been established by the findings, first of Haldane and Priestly,[1] who in 1905 showed that the rate of pulmonary ventilation was dependent upon the stimulation of the respiratory centre in the medulla by the carbon dioxide in the circulating blood, and secondly by the later observers Winterstein and Hasselbalch,[2] who proved that the stimulus thus supplied was not due to any specific property of the carbon dioxide, but simply to its acid nature, the facts being that all acids stimulate pulmonary ventilation. The extreme sensitiveness of the respiratory centre to very minute changes of the hydrogen ion concentration was further demonstrated by Haldane and his co-workers[3] in 1913. The result, therefore, of an increase of the organic acids in the blood will be a raised total acidity which will lead to an increased pulmonary ventilation, which will in turn lower the carbon dioxide content. The compensatory mechanism thus established has been well described and diagramatically

explained by Peabody[4] in a recent illuminating article, in which he shows that the normal hydrogen ion concentration of the blood is maintained by a fall in the carbon dioxide corresponding with a rise in its organic acids. The clinical importance of an understanding of these facts is self-evident. For since the fall in the carbon dioxide is directly due to the increased pulmonary ventilation brought about by the stimulus supplied by the increase in the total acidity, the whole process supplies a self-regulating and instantaneous means of control of the fluctuating chemical components of the blood stream. And since by the laws of diffusion of gases the carbon dioxide content of the blood is identical with that in the alveolar air at the same moment, an estimation of the tension in the latter is an easy method of ascertaining its content in the blood, and conversely, the amount of the organic acids present as well. That is to say, a lowered carbon dioxide tension of the alveolar air will indicate a corresponding degree of hypo-alkalinity, or raised organic acid content, i.e. "acidosis," while *vice versa*, a raised carbon dioxide tension indicates hyper-alkalinity.

The technique of obtaining samples of alveolar air was first elaborated by Haldane.[1] His method consists in collecting the air from the last part of a forced expiration, which the patient is directed to make into a rubber tube some four feet long and three-quarters to one inch in diameter, which is connected near the mouthpiece with a gas sampling tube. At the close of the forced expiration the air from it is retained in the tube by closing this off from the mouth-piece either by a valve or by the patient's tongue, and a portion is drawn off into the sampling tube for analysis. Four such samples are taken from four independent expirations, two made at the end of inspiration, and two at the end of expiration, the average of the four being taken for the result. During the experiment, as in all methods of taking the alveolar air, the nose is held closed by a clip.

The Haldane method has been used in a large number of important physiological and pathological researches, and in cases where it can be applied it remains unrivalled in accuracy

and constancy of results as yielding the exact data upon the carbon dioxide arterial tension. But the fact that its application demands a certain amount of intelligent co-operation on the part of the patient means that its use is limited to subjects who are conscious, and not too weak to give intelligent co-operation, and it is, of course, inapplicable to infants. Plesch, in 1909,[5] introduced a modification for use in those cases where the patient's co-operation could not be obtained, which is based upon the principle that the diffusion of gases in all parts of a closed space is equal, and that, therefore, continuous breathing into a closed chamber for a given time renders the carbon dioxide tension of the air in this chamber identical with that of the alveolar air.

The carbon dioxide tension of the air obtained in this way by the Plesch method is some two to six millimeters higher than that obtained by the Haldane method, and probably approximates the tension in the venous blood. It is not, therefore, so applicable as the Haldane method to strict physiological research, but it yields values sufficiently close for clinical purposes and is valuable as being universally adaptable to patients in all conditions of consciousness. Its accuracy was confirmed in 1911 in a long series of observations by Porges, Leimdorfer, and Markovici.[6] As modified by Higgins[7] and later by Boothby and Peabody[8] it has been the basis of extensive studies made at the Peter Bent Brigham and Johns Hopkins hospitals and at numerous other institutions on this continent. A good brief description of the Plesch-Higgins technique is given by Dr. Peabody (*loc. cit.*).*

From the above considerations it is thus readily seen that the estimation of the carbon dioxide tension of the alveolar

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*In practice the nose is closed with a clip and the patient breathes through a mouthpiece, which is connected with a three-way valve leading to the outside air or into a rubber bag. The subject begins by breathing the outside air. At the end of expiration the valve is turned so that the subject is connected with the rubber bag, which contains about 1 liter of air. He takes four or five rather deep and slow respirations from the bag in twenty or twenty-five seconds. At the end of the last expiration the valve is again turned and the subject connected with the outside air. Samples are then taken from the bag for analysis.

air by the Plesch method supplies a test for acidosis of such universal routine clinical application that its reduction to the simplest and easiest technique possible becomes a matter of real importance. The Plesch-Higgins method is undeniably cumbersome, for it involves carrying a litre of water to the bedside which must be used at the last moment to displace the 1000 c.c. of air which the bag is required to contain at the beginning of the experiment. In an interesting little monograph describing various time-saving devices introduced by him in his study of alveolar air at the Battle Creek Sanatorium in Michigan, Dr. Paul Roth[9] has suggested and introduced a modification of the Plesch method which adds distinctly to the simplicity of the technique. He simply substitutes, for the closed Plesch chamber, the long Haldane tube, connecting the patient by a valve below the mouthpiece with it for twenty-five seconds, during which time he is required to breathe naturally and moderately deeply in and out of the tube. This method is based on the view that the great length of tube makes that portion of it nearest the valve and mouthpiece practically a closed chamber.

I am indebted to Dr. Walter M. Boothby for the suggestion that I should follow this Roth method instead of that of Plesch in cases to which the Haldane method is not applicable, and to Dr. Peabody for the advice that the results of my observations in the use of this method controlled by that of Haldane are of sufficient interest for publication. These results are given in the appended chart. It is of some interest to note that the difference in the carbon dioxide tensions obtained in my use of the two methods is higher than those in Dr. Roth's own experiments as cited in his article—that is to say, the carbon dioxide tension was in my cases from three to seven millimeters higher by the Roth method than by the Haldane, while Dr. Roth's figures for both methods (*loc. cit.*) approximate closely to each other. The difference obtained in my experiments is similar to that noted between the Haldane and Plesch methods under the Plesch-Higgins technique. In correspondence with Dr. Roth he agrees that my higher find-

ings are probably to be explained by a greater length and diameter of tube, that used by me being 235 cm. long and 21 mm. in diameter, as against a tube used by him 195 cm. long and 16 mm. in diameter.

Personal technique. In each case referred to in the chart the patient was placed at rest in a chair and the tube was clamped to an adjacent table at a convenient level. A rubber mouthpiece with a wide flange for insertion between the teeth and lips was attached to a Carnegie Institute valve with wide orifice, the opposite end of which was inserted into the long Haldane rubber tube. A piece of fine bore lead tubing obtained at the Chadwick Lead Company, Boston, inserted into the Haldane tube close below the valve, connects the space at this point with the sampling tube below.

In performing the experiment, the mouth piece having been inserted without leakages and nose clip carefully adjusted, samples by the Haldane method were first taken. Here two large sampling tubes were used for duplicate analysis. In each tube four forced expirations, two given at the end of inspiration and two at the end of expiration, were taken by negative pressure, so that the contents of the two tubes represents the average of eight forced expirations. Between each expiration the patient was disconnected and the tube ventilated and a rest interval of one minute was provided.

The samples by the Roth method were taken at the same sitting but after a few minutes interval. The same mouthpiece was used as for the Haldane method, but it was inserted with even greater care, as leaks seemed more difficult to avoid. The patient was directed to breathe naturally, and moderately deeply, into the mouth-piece which was connected with the tube by stop-watch for twenty-five seconds. Duplicate samples were taken, the patient disconnected and the tube ventilated between each. When the results of the first tube analysis bore the expected relation to the figures from the Haldane samples (which, as stated above, were analyzed in duplicate throughout), the sample in the duplicate tube taken by the Roth method was not always analyzed.

The experiments were made at various times of the day and without reference to the patient's intake of food, and he was not always kept rigidly at rest in the interval between the taking of the Haldane and the Roth samples, facts which may account for the rather wide variation of differences as seen in the chart.

In the chart the columns under Acidosis have been inserted to add corroborative interest to the findings. It will be seen that the indications of acidosis yielded by the ammonia co-efficient correspond closely with those obtained by the Haldane and the Roth methods. For these figures I am indebted to Dr. E. H. Mason.

CHART SHOWING CO_2 TENSION OF ALVEOLAR AIR, DETERMINATIONS MADE BY ROTH METHOD WITH TUBE 215-235 CM. LONG AND 21 MM. WIDE, CONTROLS BY METHOD OF HALDANE

Date	Name and Med. No.	Sex	Age	Diagnosis	CO_2 Tension in Alveolar Air			Acidosis	
					Haldane Method (Normal = 38-40 mm.)	Roth Method (Normal = 42-46 mm.)	Difference between H. & R.	By Haldane and Roth Methods	By Ammon. Coeffic. (Normal = 4-7) %
1916							mm.		
22/3	S. B. 23837	M	27	Diabetes	26.3	32.3	5.9	+	19.5 (+)
26/3					24.6	39.4	4.8	trace	10.3 (trace)
5/4					31.4	37.8	6.4	+	13.6 (+)
7/4					18.8	23.8	5.0	++	24.3 (++)
14/4					37.8	44.3	6.5	none	9.4 trace
18/4					32.9	36.4	3.5	trace	7.2 trace
21/4					29.9	34.9	5.0	+	8.9 trace
23/4					31.3	36.0	4.7	+	5.6 none
24/5					31.3	36.6	5.3	+	9.5 trace
25/5	H. K. 24112	F		Cerebellar Tumour	39.7	48.7	9.0	none	
28/5									
27/5	W. R. 24088	M	45	Diabetes	42.0	48.7	6.7	none	15.9 (+)
					31.6	37.5	5.6	+	
30/8	A. C. 24462	M	15	Diabetes	32.0	37.8	5.8	+	11.0 (none)
28/9	R. S. 24539	M	18	Diabetes	32.7	37.7	5.0	+	10.6 (+)
1/9	N. W. 24359	M	51	Diabetes	39.0	46.8	7.3	none	6.3 none

Conclusions.   1.   The Roth method yields similar results to those obtained by the Plesch, and provides a simpler form of apparatus of easy application at the bedside and adapted for use in unconscious or difficult cases, with whom the method of Haldane is not for one reason or another applicable.

2.   The differences in the carbon dioxide tensions as obtained by these methods will depend upon the length and diameter of the tube and the length of time of the patient's connection with it.   A tube approximately 225 cm. long and 21 mm. inside diameter, into which continuous breathing has taken place for exactly twenty-five seconds, yields a sample having a carbon dioxide tension averaging three to six millimeters higher than that of Haldane's sample taken at the same sitting.   This difference approximates closely to the difference obtained in the Plesch method and would therefore appear to be a suitable calibration to adopt as a standard.

I would take this opportunity of acknowledging my deep indebtedness to Dr. Walter M. Boothby for instruction in the technique and understanding of this work throughout, and I have to thank Dr. C. F. Martin for the privilege of making these observations on patients in his hospital service, and for stimulus in the work.

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PERNICIOUS ANÆMIA—AN ANALYTICAL STUDY

BY J. KAUFMANN*

(*From the medical service of Professor Charles F. Martin*)

A study of some twenty-five cases of Pernicious Anæmia, admitted to the Royal Victoria Hospital within the last fourteen months, gives rather interesting results and tends to throw some light on the methods of treatment to be followed which give most hope for, at least prolonged, remissions.

We deal here with a disease that runs a febrile course, and which has the characteristics of good nutrition, profound anæmia, and attacking individuals in the latter part of the fourth decade of life, and tending to be fatal in over 99% of cases within 2 to 4 years. There is, unquestionably, an acute and chronic form of the illness, the former terminating very rapidly and showing no remissions, and the latter lasting a longer time, tending to be chronic, and having characteristic remissions of various length.

Our series of cases shows that women are as frequently affected as men, and that occupation throws little or no light on either etiology or the course of the disease. The maximum age of women affected was 70; the minimum age was 22; and average 51.

Amongst males, the maximum age was 56; the minimum age was 34; and average 45.

We find that the earliest age at which pernicious anæmia developed was in a young domestic, aged 22. The fact that this patient has recovered, and that there are other features of her blood picture which do not quite coincide with what we regard as a pernicious anæmia, would lead me to rather disregard this case in spite of the diagnosis of pernicious anæmia. It will be seen from the above statement that the average age

at which the patients were admitted to the hospital was somewhat higher than what is customarily stated by other authorities. This, however, may be pure coincidence of the year's admissions.

Amongst the results it is interesting to note that we have had eight deaths, that six did not improve, eight improved or developed remissions—of those eight, six had distinct remission of the disease. The average duration of the illness of those who died was eighteen months, and the average duration of the illness of all the cases that came under our notice was nineteen months at the time they came under observation.

It would seem that a high colour index was one of the most constant features in about 90% of the cases. The colour index, however, gave no indication of what the course of the illness would be like, or if present in remissions how long they would last. A disappointing feature of the blood film was a comparative infrequency of the occurrence of nucleated red blood cells. Only eight cases of our whole series showed this satisfactorily. Megaloblasts when present in large numbers seem to be indicative of a critical stage. The characteristic features of the blood were the low red blood cell count—in one case as low as 580,000 red cells per cubic millimeter—a comparatively large percentage of hæmoglobin, although in one case it was as low as 10%, and the high colour index; this did not in any of our cases reach 2. The characteristic blood film features were: marked poikiloytosis and anisocytosis, polychromatophilia, basophilic degeneration of the red blood cells, and in less than 50% of the cases erythroblasts, megaloblasts and microblasts. There seems to be little or no bearing of the white count or differential white cell count on the disease; marked lobation of the polynuclear neutrophiles was present in several cases, while 75% of the cases showed a decided relative leucoytosis. Delayed coagulation was present in a few instances.

Gastric achlorhydria seems to be, if anything, more constant in this disease than in cancer of the stomach, while several of the cases showed a distinct alkaline gastric content.

The blood pressure was invariably low in our cases, even though the disease developed in very advanced life; over 90% of the cases had a systolic blood pressure of less than 130 mm. of mercury, and the majority of them were between 100 and 120 mm. systolic pressure.

Only four cases showed hæmorrhage into the ocular fundi, pallor of the disks was not uncommon, but 12 cases showed no fundial change whatever.

There seems to be no marked alteration in the concentrating ability of the kidneys, even in the most marked cases of anæmia, and although one does come across a few instances where the specific gravity is low there was usually present some evidence of renal involvement of the nature of a progressive intersitial lesion. The classical cherry-red urine and hæmaturia were comparatively rare findings in our series; bile and urobilin were met with but rarely. The stools were normal in all cases and showed no indication of blood or parasites. The rectum was normal in all but one case, where a slight fissure was present. A vast majority of the cases showed gastro-intestinal disturbance of one form or another, manifesting itself mainly by nausea, vomiting or diarrhœa; it does not seem to us that the diarrhœa, even when protracted, had any deleterious effect on the course of the disease when otherwise favourable.

In connection with this it might be interesting to remember that certain authorities, Cabot foremost among them, are of the opinion that diarrhœa is beneficial in the course of the illness, and they go so far as to maintain it throughout the entire course of the illness.

None of our cases gave a history of syphilis, and in no case did our clinical or laboratory findings lead us to differ with the patient's statement.

The earliest symptoms of the disease consisted mainly in some form of circulatory embarrassment as evidenced by œdema, dyspnœa, pallor and cold extremities; also numbness in hands and feet, weakness, the tendency to be easily tired, loss of strength and colour, dizzy attacks, and manifestations of

gastro-intestinal disturbances as evidenced by diarrhœa, an-
orexia, nausea and vomiting. Only 7 of our cases had evid-
ences of oral infection either in the gums, tongue, or teeth; the
remarkable clean tongue is a characteristic feature of the ill-
ness. Save in the early stage of the disease the spleen
was more often small than large, while on the contrary the
liver was more often large than small.

It would seem that cases of pernicious anæmia stand
major operations moderately well. One of our cases had a
pyloro-plasty, another a gall-stone operation, and yet another
splenectomy.

With regard to the pathology of the disease it is of interest
to notice that the recent investigations of Schneider and
Eppinger emphasize that the spleen, especially in its pulp, is
very rich in blood, but the sinuses are empty. Little more
can be said of the pathology as far as the spleen itself is con-
cerned, though there are many theories. The changes else-
where observed in the body are lemon skin, very red muscles
and yellow fat, small hæmorrhages, large, flabby, empty, fatty
heart, atrophied gastro-intestinal mucosa, fatty liver, and
excessive iron pigment in liver, kidneys, and spleen, a red
hyperactive phypmoid bone marrow and sclerosis in the pos-
terior parts of the cord.

Before giving the main facts in the treatment adopted by
us, it would seem that reference to the therapeutics employed
in our fatal cases might be interesting. The six patients that
died were all at one time or another given arsacetine, Fowler's
solution, cacodylate of soda, dilute hydrochloric acid, emetine,
iron, salvarsan, saline infusions, and blood transfusions in
addition to the ordinary care with diet, hygiene and exercise.
Of the series of cases that died it would seem at present that
blood transfusions of small volumes of blood had little or no
effect on the course of the disease either one way or another.
In view of the recent work carried out by Eppinger and also
at the Johns Hopkins Hospital at Baltimore, we have adopted
a combined treatment of large weekly transfusions, followed
by splenectomy and then again by transfusions. With regard

to this treatment, it will perhaps not be amiss to lay stress on one or two essentials. The blood must be carefully tested for hæmolysis by one of the long method tests, micro- or macroscopic. It is important to remember that the essential of the test depends on one very important factor, namely: that the patient's serum must not hæmolyze the donor's red blood cells, and that a big suspension of red blood cells must be used. In the midst of the more or less hopeless course of this illness it would seem that the greatest hope for improvement rests, as far as we know at present, on the combination of the above treatment.

In connection with this I wish to quote two cases which would interest you and give you an idea of what may be accomplished by this treatment. One is a case worked out by Dr. McClure of Johns Hopkins, the results of which were given to me by Dr. Lewis, and the other a patient of Dr. Martin's at the Royal Victoria Hospital, worked out by Drs. Martin, Mason and myself. Before subjecting the patient to the splenectomy we carefully carried out an extensive series of metabolism experiments, the results of which will be published in another communication. The patient should be given a large transfusion regularly every week for several weeks before splenectomy is done. Dr. McClure's patient received 11 liters of blood before the splenectomy was done. The patient stood the operation well, and he seemed to hold the transfused blood much better after splenectomy than before. Improvement was rapid, and the patient was also given 5 liters of blood after his splenectomy. It is now seven months since the operations was performed, and the patient has a blood count of 4,750,000 red blood cells and 85% hæmoglobin. He is hard at work at his usual occupation.

In our case splenectomy was performed in September, the patient is still very well, and is at work (Jan. 1916). His hæmoglobin and red blood cells were considerably above 60%. Unfortunately we did not give him any transfusion after the splenectomy and the last examination showed that the count was going down. It would seem that the combined treatment

of massive transfusion and splenectomy, and the return of the patient for additional treatment as soon as he begins to feel weak, short of breath or develops pallor, should at least prolong the remissions and enable the patient to return to his usual work for some time. Both these cases are still alive (Jan. 1916). Additional possibilities can only be demonstrated as time goes on, and it might be suggested to keep patients under observation in hospital for two months after the splenectomy.

TUMOURS OF THE LUNG

By Rufus A. Morison

(From the medical service of Professor Charles F. Martin)

It frequently happens that tumours of the lung, perhaps on account of their infrequency, though in part, too, on account of the variability of their symptoms and signs, remain undiagnosed until the condition has been far advanced.

The following cases are placed upon record with a view to illustrating some interesting points in diagnosis which have appealed to us as of importance.

In two instances tuberculosis had been suspected for a long period of time, and in another the diagnosis of septicæmia had been the natural conclusion until late on in the disease.

Evidence of a chronic painful lesion of the lung, without cough or expectoration, is suggestive of tumours of the pleura or lung, whether primary or secondary.

The rapid and repeated recurrence of bloody pleural effusions is almost pathognomonic of pulmonary or pleural tumours, more especially when accompanied by continuous pain and dyspnœa. The nutrition may have been well maintained.

The cytological examinations of the effusions were not found to be of great diagnostic value, and in none of the cases were there any tumour cells found.

The examination of the blood was likewise of negative importance in all of our cases.

Great importance seems to attach to the use of stereoscopic skiagrams, and attention is drawn to this method of examination *after* thoracentesis, wherever a pleural effusion has occurred in an adult over 45 years of age.

Pressure signs are of the greatest value: sometimes a deflection of the œsophagus is found by Barium feedings under

X rays, sometimes the trachea has been seen to be displaced, while again the signs of pressure were such as commonly occur in any mediastinal tumour.

Pain in the back of the head from pressure of metastases on the cervical nerves was present in one case, and swelling of one arm, so common to all intrathoracic growths, was also noted in several cases.

Pathologically, these tumours were of unusual interest—in their development, their chronicity and their types. In one instance the metastases in the axilla were of a type strikingly different from the original growth in the pleura.

(1) Extensive Metastases in the Lungs from Primary unrecognized Hypernephroma. (Urine Normal)

Summary

This was a man suffering for many years (10 or more) from signs and symptoms of pulmonary and myocardial disease, with but slight emaciation. Examination of the lungs on admission revealed the presence of tumour masses, and this was confirmed by the fluoroscope, as well as with stereoscopic skiagrams.

A hypernephroma of large size was found at autopsy from which the metastases had spread to the lungs, but during life the urine had showed no blood.

In the terminal months of his illness hæmoptysis had developed, and signs of septicæmia with high irregular fever, polynuclear leucocytosis, and enlarged spleen. Subcutaneous swellings formed, resembling cold abscesses, as well as similar numerous points of osseous involvement, all of which he refused to have examined or treated.

A secondary infection with its attendant signs had obscured the real diagnosis, even to the extent of showing pus in the lung from exploratory thoracentesis.

The clinical features of interest, then, were as follows:

1. The long duration of the illness.
2. The late development of septicæmia.
3. Hæmothorax with normal differential white cell count.
4. Pus removed from the lung (secondary infection amid the neoplasms).
5. The diagnostic importance of the sense of touch from the inserted needle, and its pulsations with the heart beat.
6. Importance of stereoscopic skiagrams.
7. Subcutaneous and bony metastases (the latter revealed by skiagrams), three being peculiarly common to hyper-nephromata.

Synopsis of Case Report

CASE No. 23,928.   D., aged 45.   Male.   Carpenter.

The patient was admitted to Hospital complaining of shortness of breath.   His family history was unimportant, while his past history revealed morning cough for 20 years, but no hæmoptysis till the present illness.   Nor were there any night sweats.   Palpitation had been noted for 10 years, but there had been no œdema.   His digestion was good on admission, but for one year previously he had vomited "nearly every morning." after spells of coughing.   Three years ago he had suffered an uneventful attack of typhoid fever.

Present Illness: The present illness may be said to have begun 10 years ago with symptoms suggestive of a myocarditis. There were morning cough, slight expectoration, dyspnœa and palpitation of the heart, much increased even with slight exertion, so that it was difficult to do even light work.   Three months prior to admission, hæmoptysis came on after exertion (logging), and recurred at frequent intervals for 5 weeks, and for the past month cough and expectoration were frequent, though the blood gradually disappeared.

All the symptoms during the 10 years had progressively though gradually increased up to the time of admission, when a more acute stage of the malady was obvious.

Condition on Admission: The patient, though well nourished, was pale, perspiring freely and suffering no pain. Orthopnœa was present with paroxysms of coughing, and the sputum was pinkish in colour.

The arteries were sclerosed, the pulse rate 100 per minute, and there was slight cyanosis of the lips, but no clubbing of the fingers.

Lymphatic System: The right epitrochlear gland was enlarged, as were also the inguinal glands. The tonsils were normal.

Respiratory System: The sputum was frothy, pinkish in colour, with some clear mucus, and had a sweet odour. Under the microscope one saw many epithelial cells and white blood cells, many fine bacilli, but no tubercle bacilli. The sputum was cultivated for predominating organisms, and revealed streptococcus viridans, the pneumo-coccus (type 4), and micrococcus catarrhalis.

The thorax was well formed, and somewhat emphysematous.

The clavicles were not prominent, and the chest-wall was well nourished. The *right lung* below was immobile. *Vocal fremitus* was diminished on the *right* side at the apex, and absent elsewhere. On the *left* side in front and behind the note was dull to flatness, yielding a wooden resistance to percussion except in the interscapular region. Over the whole lung the breath sounds were faint, distant and accompanied by fine moist rales, no whispering pectoriloquy. The right lung was hyper-resonant. There was no Grocco.

The respiratory sounds were accompanied by bubbling and sibilant rales with expiration wheezing and prolonged.

Vascular System: There was no bulging, but an obvious heaving of the lower sternum. The heart was displaced a little to the left, and a to-and-from murmur was faintly heard at the aortic area. The apex was clear.

The electrocardiogram shewed a left-sided preponderance.

Fluoroscopic Examination: The heart shadow was increased to the left.

The diaphragm moved normally on the right side. On the left side a dark shadow was seen in the upper left lung, evidently due to consolidation of the lung.

Stereoscopic pictures showed a mass filling the left lung. The apex seemed solid, and stood away from the chest wall like a dome. A mass, too, could be seen in the centre of the right lung.

Blood Examination   Differential Count (Jenner):

R.B.C.	3,555,000
W.B.C.	17,800
Hb	70%
Polymorpho-nuclears	79%
Polymorpho-eosinophiles	1%
Polymorpho-basophiles	1%
Mononuclears, small	11%
Mononuclears, large	5%
Transitionals	3%

Wassermann negative.

Digestive System: Caries of the teeth and pyorrhœa were marked. The abdominal wall was well nourished, and the abdomen was distended, but there was no fluid.

The spleen and liver were normal on admission. The rectum was normal.

Locomotor System: The locomotor system was normal on first examination, no exostoses. On the head there was a fatty-like tumour, 4 x 5 cm. in diameter, which did not move with the scalp, appearing not like a wen, nor as a lipoma, but had rather a soft cystic feel.

The urine was repeatedly examined. A trace of albumen was usually present, and a few casts, but *blood was never found* on repeated examinations. Nycturia, however, had been recorded for several months prior to admission.

Diary. April 23, 1916. Exploratory puncture in the 10th left interspace yielded 10 c.c. of a cloudy yellowish fluid containing 24,000 cells per cubic mm.

Differential cell count of fluid:

P.M.N. cells	53%
L.M. cells	3%
S.M. cells	6%
Endothel. cells	1%
Erythrocytes	29%
Degenerated forms	8%

April 24, 1916. Thoracentesis yielded only 100 c.c. of fluid, which clotted quickly. The fluid was difficult to locate.

Increasing dyspnœa gradually supervened, suggesting the need of further thoracentesis, which was performed one week later. The *needle* went in behind with a little difficulty until it passed the parietal pleura, when it *encountered very tough lung,* and was carried further only with difficulty.

The pulsations of the heart were readily conveyed to the needle, which described small circles with each heart beat.

On exploring in the mid-axillary line, at the 7th interspace, the needle encountered tough resistant lung tissue. Only a small amount of fluid was obtained at this time.

May 6, 1916. A small lump 2 cm. in diameter appeared at the inner edge of the left eyebrow. It was disc-shaped, soft and with a definite margin, fixed to the deep structures.

A similar lump appeared about the margin of the heart, about 1½ cm. in diameter, and again another lump on the radius of the left arm about its middle and on the upper 3rd of the right femur. These lumps were fixed to the deep structures, and did not move when the limb was in motion.

Skiagrams of these bones showed small worm-eaten holes at the region of each lump and elsewhere, as though from the presence of bony abscesses. There was no glandular enlargement, except that noted on first examination.

Operation was suggested for diagnosis, but was refused.

Gradually slight œdema of the lower extremities and back developed, but the glandular enlargement was no greater than on first examination.

May 18, 1916. Exploratory thoracentesis was again performed in the posterior axillary line at angle of scapula. The lung was found to be very tough and resistant to the exploring needle. When, however, the needle was pushed about 8 cm. into the thorax, a *thick yellow pus was aspirated from within the mass* with a differential count of $97\frac{1}{2}\%$ polymorpho-nuclear cells.

May 24, 1916. The patient died suddenly of cardiac failure.

AUTOPSY—IMPORTANT FEATURES

The body is that of a moderately developed male, 170 cm. long, and whose apparent age is 45 years. Nutrition is fair.

There is a *nodular mass above the eyebrow in the left frontal region, about the size of a marble.* The skin is soft and elastic. No œdema. Eyes show slight jaundice. The teeth are fairly well preserved, except for a few missing. The gums show pyorrhœa ʿalveolaris. *Small marble-sized firm mass in the extensor muscles of the left forearm.* The chest is barrel-shaped. The abdomen is flat. External genitalia normal. The lower limbs are well developed.

General Points. On opening the abdomen the liver is 8.5 cm. below the ensiform. The dome of the diaphragm is at the level of the 4th space right, and 5th rib left. There is no free fluid. The omentum is large and fatty, and spread completely over the intestines, which are moderately collapsed.

Circulatory System. Heart: Weighs 440 grm. Visceral pericardium is smooth and glistening. There is increased amount of subpericardial fat. The right side of the heart is collapsed, contains ante-mortem clot; the left side contracted. The musculature is dark red with lighted mottled areas and is lightly friable. *The cusps of the aortic and mitral valves show slight thickening. The first part of the aorta shews advanced atheromatous changes.* The coronary arteries show early fatty changes. The tricuspid orifice measures 14 cm., the pulmonary orifice 7.5 cm., the thickness of the wall of the right ventricle 1.2 cm., and the left 2 cm.

Respiratory System. Right Lung: Weighs 1380 grm. It is voluminous and retains its shape on the table. Pleura is smooth and glistening, is mottled greyish red, and scattered through there are larger and smaller firm nodules of a yellowish colour. The lung is moderately crepitant throughout, except dependent parts which are less so. On palpation, nodular masses varying about the size of a marble can be palpated.

On section, the cut surface exudes a yellowish red fluid, and scattered throughout are the nodules described above. Between the nodules the surface is a dark red colour and smooth. The mucous membrane of the large bronchi is congested.

The *left pleural* cavity is obliterated, the pleural surface covered with fibrinous exudate. The colour is a reddish grey. Lung non-crepitant. On section the cut surface shows numerous nodules (see right lung) scattered throughout the intervening lung tissue, granular and greyish red in colour. The bronchi are thickened and dilated, and on pressure exude thick, creamy, purulent exudate. Mucous membrane of the bronchi congested, and lumen full with purulent exudate. The left lung weighs 1480 grm.

Digestive System. Stomach: The rugæ well marked. Mucous membrane is covered with rather mucoid material. Pylorus is free, common bile duct patent.

Liver weighs 2200 grm. It is rather flabby, capsule thin and smooth, edges rounded. There are *two small pea-sized nodules* seen beneath the capsule. On section the cut surface is moist, normal markings indistinct. There is a *nodule the size of a pea,* yellow colour, near anterior surface.

The *gall bladder* is moderate in size and filled with dark green fluid bile.

Pancreas: Is rather large, moderately firm, and lobules well marked.

Spleen: Is rather flabby, capsule is thin and smooth. On section the cut surface is deep purple colour, the Malpighian corpuscles plainly visible, the splenic pulp friable. *The organ weighs 230 grm.*

Lymph Nodes: The retroperitoneal gland near the upper pole of the left kidney size of a walnut, firm on section; the surface is mottled with greyish red and black areas. The peribronchial glands are all enlarged and anthracotic.

Adrenals: The left is thick and nodular. On section shows a growth the size of a marble and several small nodules. The right shows several small similar nodules.

Kidneys: The *left* weighs 620 grm. It is about three times the normal size, and surrounded by a large amount of fat. Somewhat U-shaped, thick and bulky. The capsule strips easily; the upper pole of the kidney is involved by a large tumour, the surface of which is nodular, whitish yellow with dilated venules. The remaining surface of the kidney has pea-sized nodules scattered throughout; its surface shows marbling (dark grey and red). On section the upper two-thirds of the kidney are involved by the growth which is nodular and lobulated, of pale yellowish colour, and shows extreme softening at the extremity of the pole. The lower pole shows dark red kidney substance. There is a considerable amount of pelvic fat.

The *right kidney* weighs 180 grm. It is of about normal size and shape, and rather flabby. Capsule thin and strips easily. Kidney surface is smooth and stellate veins dilated. There are *several small, firm, yellowish* nodules scattered over the surface. On section the cut surface is dark red. Differentiation between the cortex and medulla is poor. Glomeruli stand out as pin-point red dots.

N.B.—Histological examination of the growth showed pictures typical of the so-called Hypernephromata.

(2) Intrathoracic Sarcoma (of Mediastinal Glands) involving the Left Lung

Summary

Here was a patient æt. 29 years, profoundly weak and emaciated on admission to hospital, and complaining of epigastric pain. She was almost aphonic. She stated that her

illness was only of three months duration, and that the earliest signs were pain in the side of the head and neck. Thoracic signs soon developed, with dyspnœa, painful swelling of the left arm, and with engorgement of the left cervical veins. There was no cough.

An existing pleural effusion was tapped, and physical signs revealed evidences of a neoplasm of the mediastinum. The fluoroscopic examination confirmed this, and a barium drink showed obstruction and deflection of the œsophagus at the aortic arch. The left cervical glands became enlarged, and the asthenia rapidly developed to a fatal result.

A mass was felt in the right hypochondrium, and hæmaturia was found on admission. For this reason a hypernephroma was at first suspected, and the presence of some bony new growths on the clavicle and femur seemed to confirm this idea for a time.

Clinical Features: The chief clinical features of interest in this case are as follows:

1. The short duration of the symptoms.
2. Their resemblance to hypernephroma, because of a mass in the right hypochondrium, the hæmaturia, and signs of bony involvement.
3. Headache an early feature (pressure on cervical nerves), soon followed by the pressure signs in the vena cava, subclavian vein, left recurrent laryngeal nerve, and the œsophagus.
4. The importance of fluoroscopic examination with barium to note deflections of the œsophagus, and signs of obstruction.
5. The negative results of the examination of the pleural fluid and of the blood.
6. The importance of examination of the glands.
7. The presence of hæmo-pericardium (at autopsy).

SYNOPSIS OF CASE REPORT

CASE No. 23,376. M. C., aged 29. Female. Laundress. Single.

The patient was admitted to the hospital complaining of pain in the stomach. Her family history was good, and her past history disclosed nothing of importance, except a pleural effusion 14 years ago, without any history of chronic cough or expectoration.

The Present Illness: The present illness began 3 months before admission, with severe pains in the left side of the head on lying down.

There was also some pain in the back about the dorsal and lumbar region, radiating down the leg to the external genitalia. The pain had lasted 10 weeks, off and on, and was relieved only by the left lateral decubitus. Shortly before her admission to hospital the epigastric pain and tenderness appeared, without any vomiting or other signs of gastric disease. These symptoms had persisted without any further development until a few weeks before her admission, when for the first time there appeared evidences of thoracic trouble.

Dyspnœa, then, was a late sign, and with it came some slight dysarthria (paralysis of cord), pain and swelling in the arm, and dysphagia, but at no time any productive cough.

Physical Examination: Physical examination showed the patient to be much emaciated and prostrated, with dyspnœa that was accentuated by tracheal rales, and the patient seemed from time to time to be *in extremis.* The left cervical and left axillary glands were slightly enlarged.

Respiratory System: Examination of the respiratory system was of great interest. The thorax was long and flat, the ribs visible, the clavicles prominent, and the apex retracted more on the right side than on the left.

The physical signs were those of a moderate left pleural effusion with displacement of the heart, and above the effusion were large areas of dulness with resonant lung between them. Flatness existed over the sternum in its upper third.

Marked tenderness was found in the right costochondral junction of the 5th and 6th ribs.

Cardio-vascular System: There was marked cyanosis of the face, with engorgement of the veins of the neck, as well as

of those of the left hand; but there was no clubbing of the fingers, and no capillary pulse.

Pulse 128–95; the vessel wall was somewhat thickened, but the pulse itself was full, regular and equal on both wrists.

There was no præcordial bulging.

The right border of the heart was 7 cm. to the right of the mid-sternal line. The sounds were normal.

The abdomen was rigid but flat, while a *large mass* was palpable in the right hypochondrium and flank, apparently the liver, with a hard edge and nodular to the feel, one large nodule being about the size of half an egg in the mammillary line. It was slightly tender and movable (? right kidney).

The liver filled the epigastrium, where it was extremely tender, and still more tender in the left hypochondrium.

Percussion over the mass was dull, while elsewhere the note was tympanitic.

The *rectal examination* was negative.

Locomotor System: There was some tenderness over a bony elevation on the anterior surface of the right femur.

On the right clavicle there was also a definite projection at the junction of the outer and middle 3rd, and a smaller projection at the costo-sternal junction of the 1st rib (? metastases or exostosis).

Nervous System: The nervous system was normal.

Phonation was poor, the patient speaking in a loud whisper with a slight tone, and a laryngoscopic examination revealed paralysis of the left vocal cord.

Fluoroscopic Examination: The fluoroscopic examination of the chest revealed a shadow indicating pleural effusion, but no satisfactory picture was obtained at the time owing to the patient's condition.

Wassermann tests on the blood and spinal fluid were negative.

The *blood* examination shewed a slight secondary anæmia, and the differential count was practically normal.

Thoracentesis was performed a few days after admission, and 1395 c.c. of bloody fluid were removed; specific gravity 1019, albumen 18 grammes to the liter.

Cell Count...................... 12,200
R.B.C........................... 25%
Mononuclears.................... 3%

The *fluoroscopic examination* now revealed the left lung clearer.

The heart was less displaced, but the peribronchial tissue was very dense.

The diaphragm was movable on both sides.

A barium drink was given, and showed *obstruction at the arch of the aorta*, where the mediastinum showed a definite shadow, but was elsewhere normal.

The *urinary examination* shewed a trace of albumen, red blood cells on repeated examinations, and a few white cells; otherwise no abnormality.

The *phthalein tests* shewed 52% on examination in two hours.

Lymph Glands: A few days after admission the chain of glands, hard and shotty, became palpable above the clavicle, just outside the sterno-cleido-mastoid muscle on both sides.

The veins in the neck became larger, as did also those of the arm and supra-clavicular of the same side.

Respiration became progressively more laboured, and the abdominal pain increased. The patient died a few days after admission.

Synopsis of Autopsy Findings

The autopsy revealed a primary lympho-sarcoma of the mediastinal glands, with extensive invasion of the lungs in both lobes; hæmo-pericardium and hydro-thorax.

There were metastases in the pericardium and myocardium, as well as in the pancreas, liver, and periportal glands. The adrenals presented no gross lesions.

The kidneys were normal.

The growth had spread in a fan-shape from the mediastinum towards the periphery of the left lung, forming a huge series of nodules. The right lung was free from involvement. The growth, however, pressed upon the roots of the lungs, upon the trachea, and the left recurrent laryngeal nerve.

The bony points recognized clinically were found to be exostoses, and not connected with any new growth.

Histological sections of the tumour showed the cells to be lymphoid in type with active division, and held together with a small mass of reticulum.

(3) Endothelioma of the Pleura with Metastases in the Lungs, Heart and Pericardium. Hæmo-pneumo-thorax

Summary

Here was a man æt. 57, whose illness began 13 months before death with signs of a pleural effusion, without cough or expectoration.

Tapping was followed by rapid reaccumulation. This was repeated at intervals on 10 different occasions, the fluid being always bloody. Tuberculosis had been diagnosed and confirmed by a positive tuberculin reaction. The temperature had been irregularly intermittent; there was some wasting after thoracentesis, and the fluoroscopic examination revealed a persisting shadow on the right side at the level of the 2nd, 3rd and 4th spaces.

Pain in the right side, slight at first, gradually increased, as did also the dyspnœa, in spite of tapping. Pneumo-thorax developed, and the heart, previously displaced by fluid, later seemed fixed.

Progressive asthenia developed to a fatal issue.

The autopsy revealed a hugh endothelioma of the pleura, with involvement of the right lung and pericardium. An old foccus of Tbc. was found at the right apex.

The Clinical Features of interest were as follows:

1. Dyspnœa and thoracic pain were the earliest symptoms, with persistence and increase of pain. The early appearance of an effusion masked the original neoplasm.
2. The hæmo-thorax recurred rapidly and frequently.
3. Pneumo-thorax developed. Fixation of the heart was an indication of adhesions or neoplasm.
4. There was some resemblance to tuberculosis-fever, loss of weight, positive tuberculin reaction, and hæmo-thorax.
5. Fluoroscopic findings after thoracentesis were significant.

CASE No. 13,361. T. B., aged 57. Male. Painter. *Admitted* to the R.V.H. April 29, 1915. *Died.*

The Family History: The family history was not important, and the past history was good.

The Present Illness: Began 13 months before death, with shortness of breath, the result of a pleural effusion.

During the first 4 months the patient was tapped on 10 different occasions, with rapid re-accumulation, the fluid at each operation being bloody. Tuberculosis had been diagnosed, and it had been confirmed by a positive tuberculin reaction.

The temperature early in the disease was characterized by remissions, after tapping, and exacerbations, up to the time of accumulation of fluid. There was moderate pain over the affected area.

Physical Examination: Showed the patient to be fairly well nourished, and in no serious pain.

The muscles were *flat*, there was no œdema, and the reflexes were all normal.

The *lymphatic glands*, while palpable, were not appreciably enlarged, except in the right supra-clavicular region.

The *thyroid* was normal.

Examination of the thorax showed a deep right supra-clavicular fossa, while the infra-clavicular region on either side was flatter than on the left. With each inspiration the right side was practically immobile, while the movements of the left side were somewhat exaggerated.

Fremitus was diminished on both sides, and quite absent over the lower half of the right chest.

The percussion signs were unusually interesting. With the patient lying down, there was flatness over the whole right lung, with the exception of a small area to the right of the sternum, which was slightly hyper-resonant. On sitting up this area became flat, the change occuring each time even with rapid alteration of position.

The left lung was hyper-resonant throughout. The breath sounds were diminished over the whole right lung, except in the area of resonance in the 2nd interspace, when the patient was prone; this area, too, became silent with inspiration when the patient assumed a sitting position. A few fine moist rales could be heard over the whole right lung, while the sounds over the left lung were normal.

The Cardio-vascular System: The pulses were equal on both sides.

The blood pressure was 118–86.

The heart was displaced to the left, 15 cm. to the left of the midsternal line.

The sounds were distant but clear.

Alimentary System: The only features of importance were caries of the teeth, a palpable liver, but no other sign of disease in any of the viscera or cavities.

The Genito-Urinary System was free from disease.

Fluoroscopic Examinations before removal of the fluid disclosed a shadow over the right pleural cavity throughout, but on removal of over 1 liter of fluid the upper portion of the chest became more pervious to the rays, but a very *dark shadow was found in the 2nd, 3rd and 4th* spaces just to the right of the sternum.

This examination proved of great significance in reaching a diagnosis of the condition.

The fluid from the pleural cavity was bloody, with a specific gravity of 1011, alkaline reaction.

Blood Examination: *Differential Count* was as follows:

      Polymorphonuclears.............. 72%
      Polymorphoeosinophiles.......... 4%
      Small lymphocytes............... 16.1%
      Large lymphocytes.............. 4%
      Endothelial cells................ 7.5%

During the patient's stay in hospital the dyspnœa became more marked, the pain increased in the right side, but there was comparatively slight loss of flesh.

After a second tapping, pneumo-thorax was found, but as time went on the heart was less and less displaced by the fluid or air, evidently becoming fixed by adhesions or new growth.

AUTOPSY

The autopsy revealed several features of importance. On opening the thorax the whole right side was represented by a cavity with a thick granular membranous lining, and filled with blood-stained fluid.

The right lung itself was seen as a firm mass, the size of a normal kidney, with a thick, firm, white fibrous capsule, the whole being firmly attached at the upper part of the thorax, a cavity leaving a very large præcordial space.

The left pleural cavity was practically free.

The heart, which was normal, was bathed in a large amount of bloody fluid (hæmo-pericardium), while the pericardium itself was thickened, fibrous-looking, and dotted over with a large number of nodular growths, which were likewise firm and fibrous-looking.

In other respects the autopsy revealed nothing of great importance, except the presence of some old caseous nodules in the apex of the right lung; extensive tuberculosis of the peri-bronchial glands, which were much enlarged; a few duodenal ulcers; but nowhere else any sign of metastases.

Histological examination of the pleura showed marked hyaline fibrous tissue thickening. Within this fibrous tissue rest alveolar structures partly lined and partly filled by rather high, epithelial-like cells. Within the lumen of these irregular

alveoli the cells appear flatter. The growth stops short of the lung itself, which is not involved. In some of the dilated lymphatics the character of the cells appears lower and they distinctly line the wall. In others, however, a gradual swelling and almost mucoid protoplasm of the lining endothelium may be seen. One can gradually trace these lymphoid channels to more definite alveoli.

These alveoli, therefore, must be regarded largely as being dilated lymphatics filled by tumour cells.

The sections from the pericardium showed a very similar involvement to that of the pleura. Here also almost glandular-like, but in places diffuse, growth of small endothelial-like cells is plainly shown, and the alveolar arrangement is produced by the gradual dilatation of lymphatics within which these cells grow and progress.

Diagnosis: The case was, then, one of *Endothelioma of the Pleura, with Secondary Involvement of Pericardium and Atrophy of the Lung,* in which the clinical course, on careful analysis, showed the presence of some new growth in the chest, but in which there were also signs sufficient to justify a diagnosis of *Fibroid Phthisis.*

(4) Endothelioma of the Left Pleura, involving the Pericardium and the Lymph Glands of Axilla. Hæmo-pneumo-thorax.

Summary

This patient, æt. 43, had been ill 2 months with left-sided thoracic numbness, developing into pain.

For 6 weeks no other sign supervened, when severe headaches followed, with progressively noticeable dyspnœa and chilliness.

On admission he was fairly nourished, had intermittent fever and left pleural effusion, with dislocation of the heart to the right. Thoracentesis removed 900 c.c. of bloody fluid with lymphocytes predominating. The fluid rapidly recurred, and

was frequently removed to relieve distress. In all, 29 liters were taken away.

Pneumo-thorax developed after a time and it was noticed that the heart, as in Case 3, became fixed.

A few *glands*, palpable in the left axilla and neck on admission, were noted to be increasing in size. One was removed and examined by Dr. Oertel, and the diagnosis of *adeno-carcinoma* was established.

Fluoroscopic examinations repeatedly showed shadows on the lung, but a subsequent stereoscopic view showed still more clearly that the left pleura was markedly thickened, as was the mediastinal tissue, and that a patchy area existed in the right lung, while the left seemed compressed and thickened.

Progressive weakness developed and patient died several months after entrance, the diagnosis being an adeno-carcinoma of the lung or bronchi, with metastases.

At the autopsy the lesion was found to be a pleural endothelioma without pulmonary involvement.

The features of special clinical interest were as follows:

1. The persistent pain lasting several months, starting over the lung and coursing down the left arm. This was the only sign for many weeks.
2. Persistence of headache as an early sign.
3. Late development of pressure signs and venous stasis.
4. The presence of hæmo-thorax recurring rapidly and frequently after aspiration. (In this case 29 liters in all were removed during the course of the disease.) Development of pneumo-thorax.
5. The involvement of axillary glands, whose examination determined finally the diagnosis, though the primary focus differed histologically from the glandular metastases.
6. The heart was dislocated to the right and fixed in that position.
7. Hæmo-pericardium was found at autopsy.
8. Tuberculosis was at first diagnosed, and the signs were naturally misleading. Intermittent fever was present

and the blood pressure was constantly low.   The tuber-
culin reaction was positive.   The effusion was bloody
and showed pleolymphocytosis.   It was noted, too, that
the tuberculin reaction was followed by increasing
hæmorrhage into the pleura.

Synopsis of Case Report

CASE No. 23,312.   J. J., aged 43.   Married.   Fireman.

Admitted to hospital complaining of pain in the chest and
shortness of breath.

The *Family History* was negative, and the past history
unimportant.

The *Present Illness* began 2 months previously with pain
in the left side of the chest and was characterized at first rather
as a numbness, which was relieved by pressure.

This remained the only symptom for 6 weeks, after which
severe headache developed for several weeks, followed then by
chilly sensations and some dyspnœa on exertion, which became
progressively worse.

Physical Examination: On admission he was found to be
a well nourished man with no evidence of anæmia, and with no
apparent pain.

Lymphatic System: The left axillary, inguinal and femoral
glands were palpable.

Respiratory System: The thorax was symmetrical and
well developed, though the left side moved somewhat less than
the right, and showed the usual signs of a large pleural effusion.

The right lung was normal on examination.

There was at this period no other noteworthy sign on
examination.

Vascular System: The pulse was equal on both sides.

The heart was dislocated 7.5 cm. to the right of the mid-
sternal line, while the left border could not be defined on ac-
count of the fluid in the pleura.

The heart sounds were normal.

In the abdomen there was nothing of importance except that the edge of the liver was palpable.

Rectal examination revealed nothing.

The *Nervous System* was normal.

Diary. Thoracentesis was performed, and 900 c.c. of bloody fluid was removed from the left pleural cavity. This fluid was carefully examined, and no tumour cells were found. 20% of the total cell count consisted of red blood cells, while the differential white cell count showed:

Small lymphocytes................ 95%
Large   " 3%
Polymor. nuclears................8/10%
Polymor. eosinophiles.............4/10%

The hæmoglobin was estimated at 103.

No bacilli were present, nor did an inoculated guinea-pig respond. From that time on, thoracentesis was frequently done, the fluid collecting rapidly and causing great distress and pain. Altogether 29 liters were removed.

Two months after admission 3,223 c.c. of fluid were removed, on one occasion, and the heart which was displaced to the right did not subsequently return to its normal site, being now evidently fixed in its new position. It was on this occasion that a succussion splash was heard, showing, with other signs, the existence of a pneumo-thorax.

Three months after admission a sub-pectoral gland about the size of a pea, hard and enlarged, was palpated on the left side.

Fluoroscopic Examinations were repeatedly made, and showed the lung never fully distended. Later on a *stereoscopic skiagram* was made, and revealed the pleura of the left side markedly thickened, and the apex of the left lung seemed compressed and thick. There was also a solid area in the right lung, continuous with dense, thickened mediastinal tissue.

The heart, too, showed some displacement to the right.

During the patient's stay in hospital, gradual progressive emaciation became more severe and more persistent, and was increased by a troublesome cough.

The very little sputum which was raised contained no tubercle bacilli. Vomiting supervened occasionally and the patient suffered from choking sensations.

The *pulse* varied from 96–128, and the *respirations* from 20–30. while throughout the illness the *temperature* ran a more or less intermittent course (99–102°).

The *urine*, while somewhat diminished at first, remained fairly copious until the end of his illness. It was free from abnormal elements until shortly before his death.

The *stools* were negative.

A *tuberculin test* given shortly after his admission to the hospital was followed by a *pronounced reaction*.

The *Wassermann* reaction was negative.

Towards the latter part of his illness the veins of the neck, hands and arms were engorged, and *this engorgement diminished considerably under each aspiration.*

One month prior to death, the axillary glands on the left side became slightly enlarged and hard, and one of these was excised and carefully examined by Professor Oertel. His report was as follows: "Sections from axillary glands show that the whole gland is replaced by an irregular adenomatous growth made up of variously sized and shaped acini, which are lined by, and found filled with, high epithelium with a clear, occasionally mucoid protoplasm, and whose nuclei stain deeply. Where these cells and acini appear better developed and in more typical arrangement, they resemble closely mucoid glands."

Diagnosis: Adeno-carcinoma of the lung, probably from secretory glandular tissue (bronchi).

The patient died 4 months and 17 days after admission, —that is, 6½ months from the onset of his illness.

Notes from the Post-Mortem by Professor Oertel: *Endothelioma of the Left Pleura and pericardium with metastases in the axillary glands. Pneumo-hæmo-thorax. Hæmopericardium.*

The left lung was represented by a small mass of dark lung tissue, occupying the upper portion of the left side of the thorax,

surrounded by a thickened pleura, averaging 8 mm. in thickness, of a dense, white, fibrous appearance. The parietal and mediastinal pleura were tremendously thickened, and formed a cavity containing air and hæmorrhagic fluid.

The parietal pericardium was adherent to the pleura, and showed a number of nodular masses of yellowish white appearance, irregular in outline, varying in size from .5 cm. to 1.5 cm. in diameter.

At the apex of the left lung there was a cyst, its wall formed by thickened pleura, the whole being in size equal to a billiard-ball, and its fluid contents yellowish in colour, and oily in consistence.

The bronchi showed no signs of new growth, nor was there in the lung itself any indication as to the origin of the tumour.

In the abdomen there was nothing abnormal, nor any sign in the viscera of new growth.

The Histological Picture was of great interest. In the pleura there was extensive fibrous thickening, with groups and nests of large and small flat, polygonal epithelial or endothelial-like cells, with deeply staining nuclei, showing evidence of active divisions. Careful study of the character and growth of these cells leads to the conclusion that they are of endothelial derivation and follow lymphatic and tissue spaces. These cells are also found in the lymphatics of the compressed underlying lung.

The growth in the pericardium was of a similar character.

The sections of the cyst-wall resembled those of the pleura.

The section from the axillary gland had much more glandular character (like the sections from excised gland during life), and the cells of the alveoli were high and more cylindrical, but those that had desquamated into the lumen were pale, clear and often resembled mucoid cells. Sections of the lungs in various parts showed no evidence whatsoever of new growths. ————

NOTE BY PROFESSOR OERTEL.—From a careful study of the autopsy findings, I am convinced that my first diagnosis of adeno-carcinoma of the lung, made from sections of an ax-

illary gland excised during life, was wrong, but that the primary growth is an endothelioma (or mesothelioma) of the pleura which in the gland metastasis has assumed a glandular type and acinar arrangement. Clear, high, (cylindrical) and " mucoid " cells in these metastases (which largely misled to the original diagnosis) must, in the light of more conclusive evidence, be regarded as unusual and peculiar (serous, partly degenerative ?) forms of endothelium.

EXPLANATION OF FIGURES

Fig. 1. Microphotograph of section of axillary gland removed during life: irregular glandular, adenomatous loops lined and filled by clear, high cells, often containing " mucoid " material (stained light blue in haematoxylin-eosin sections).

Fig. 2. Section from pleural tumour (autopsy): small flat (endotheliomatous) cells in lymphatics and tissue spaces of thick, cicatricial tissue.
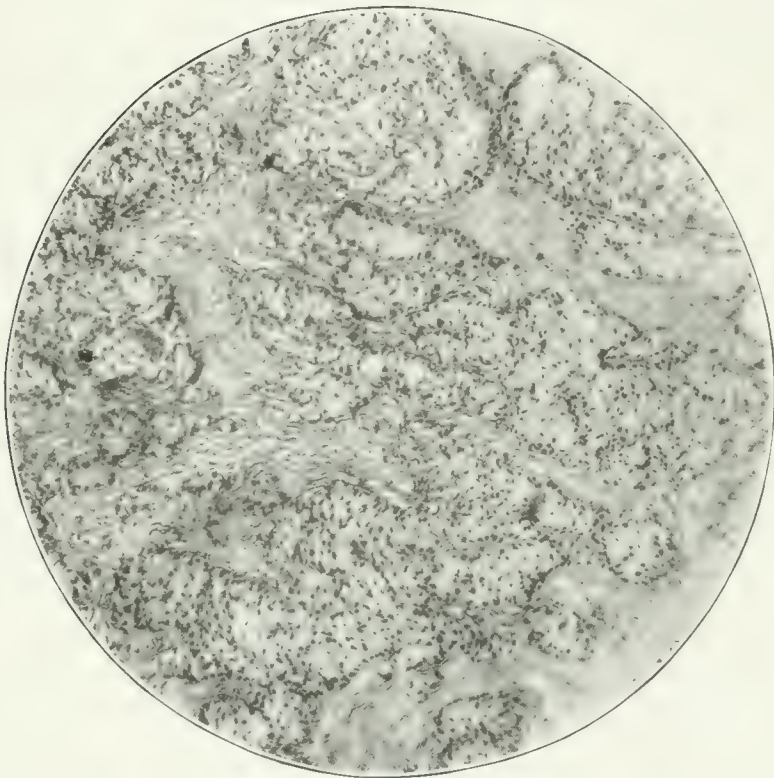
Fig. 1
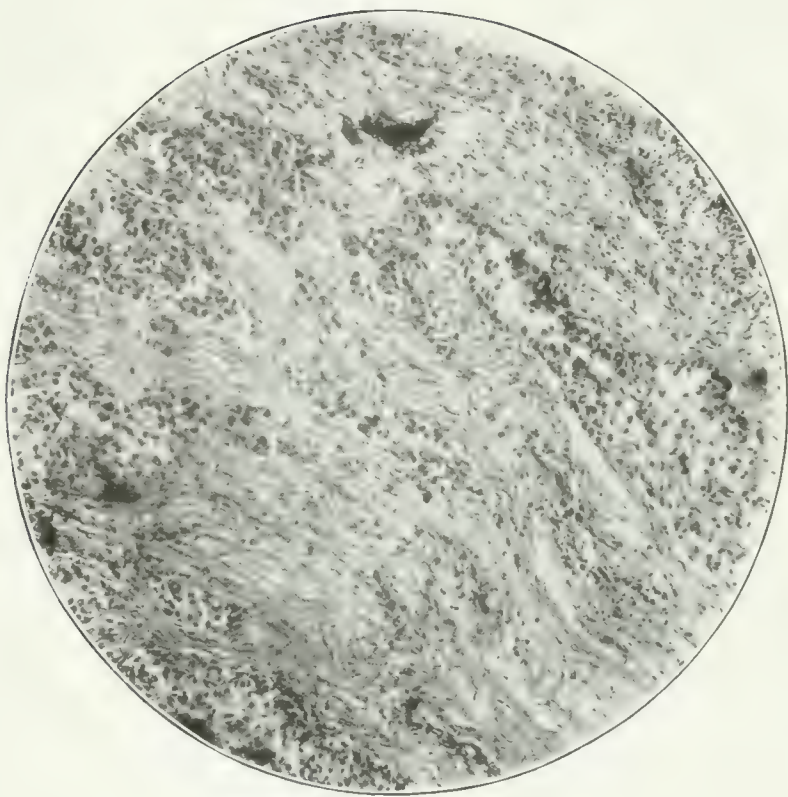
FIG. 2

A CASE OF BENIGN LEIOMYOMA OF THE ŒSOPHAGUS OF UNIQUE SIZE

By J. Kaufmann and C. T. Crowdy

(*From the medical service of Professor C. F. Martin and the Pathological Laboratories*)

Clinical History

S. C.. male, aged 29, was admitted to the Royal Victoria Hospital on March 16, 1916, with the following complaints: *Cough, Expectoration, Pulmonary Tuberculosis.*

Personal and Family History: In his family history there was nothing noteworthy, and no history of tuberculosis in remote or immediate members of the family. In his own history the patient has passed through measles, mumps, and whooping-cough at the age of five years, and at that time also had slight rheumatism. He has had a cough every winter, but never had pneumonia. During the past seven years patient has been subject to headaches and dizzy attacks, with nothing definite to account for them. Patient has always been short of breath, has always perspired freely, especially on exertion, but there have been no night sweats. For the past eleven years patient has been vomiting after meals, the material vomited being the food just taken, never any blood, but he rarely passed a day without vomiting. This vomiting usually came late after his meals and most commonly at the end of the day. Constipation has been the rule for the last four years, not, however, very marked. He has been subject to slight attacks of diarrhœa two to three times a day every three to five months. No urinary symptoms. No venereal disease. Best weight was three years ago—150½ lbs.; weight now 125 lbs. No melena, no blood in the vomitus, occasional blood in the sputum, no œdema.

Since the age of five years patient has had a cough every winter with shortness of breath on exertion, and at the age of five there were a few small clots of blood in his sputum. Some four and a half years ago he developed swelling of the knees and legs, the right limb being more affected than the left. He was ill at the time for two months; when he attempted to walk his knees got so sore that he had to go to bed and was obliged to stay in bed for six months more. Four years ago he developed a dry cough, and he once again expectorated about a table-spoonful of blood. There was considerable pain in both sides of his chest, and about this time thoracentesis was done on the right side, but no fluid was obtained. At this time shortness of breath on exertion was marked and he perspired easily. Since this time he has had a moderately productive cough, swelling of feet, legs, and knees, with distinct pitting of the skin on pressure. The joints were not red and he was able to walk about. This state of affairs continued until about five months ago, when his legs became more swollen, the pain in the knees more marked, and he was obliged to take to bed once more. Three months ago his temperature went up to 103, five weeks ago the cough got much worse, expectoration became profuse and purulent (about 12 ozs. a day) and quite abundant blood. At present his worst complaint is cough, expectoration, weakness, fever, marked loss of weight, occasional profuse night sweats, lack of appetite and a general feeling of depression.

Patient at this time consulted one of us (K.) with a view to being admitted to a tuberculosis sanitarium, having been told by his physician that he was suffering from tuberculosis of the lungs. However, an examination of the sputum showed no tubercle bacilli, and as the physical signs did not accord with a tuberculous lesion of that duration the patient was advised to go to hospital for further investigation. An X-ray, taken before admission to the hospital, also made the diagnosis of tuberculosis doubtful.

EXAMINATION ON ADMISSION—GENERAL CONDITION

Patient a tall, rather thin, man—looks about five years older than stated age. Not suffering pain, coughs a great deal, bringing up a whitish phlegm of a sweetish odour. Neck is long and thin; the veins are prominent; the thyroid is slightly enlarged; and the thyroid cartilage is prominent. Clavicles are prominent; the chest is thin; interspaces depressed; eyes somewhat sunken; cheeks flat; buccal cavity healthy; marked clubbing of fingers; and a slight bluish tinge of the ears, lips and fingers. Bones large and thick. Feet large. Ends of long bones large and thick. His gait is normal; his skin is hot and moist; and altogether he gives the picture of a very sick man.

Lymphatic System: All superficial lymph glands are slightly enlarged, soft, freely movable, and not tender. The thyroid gland is palpable, soft, slightly granular, and not tender. The tonsils are slightly enlarged.

Respiratory System: Restriction of chest movement on right side; left side somewhat full as compared with right; slight retraction of upper chest. Rather prominent sternum, scapulæ, clavicles, and ribs. Expansion generally is poor. The upper half of the right chest displays a markedly increased vocal fremitus, the lower half of the right chest an absent fremitus, the entire left chest with a slightly increased fremitus. Percussion shows a markedly wide mediastinum, $3\frac{1}{2}$ inches across in the region of the second rib, extending evenly to the right and left of the mid-sternal line, perhaps slightly more to the right. This area of dulness continues downward and to the right, passing through the 4th chondro-costal junction, and from there downward and outward in a sweeping line, crossing the 5th space in the anterior axillary line. In the axilla and upper and outer portion of the chest the percussion note is distinctly hyper-resonant. The percussion note on the left is normal, a portion of the mediastinal dulness fusing in with the heart dulness. Behind, the percussion note on the right side is impaired downward as far as the 9th dorsal spine, and then becomes flat and runs in the direction of the crest of the ilium.

The left side behind gives normal resonance. Auscultation shows a marked prolongation of expiration over the area of impairment on the right in front, and distinctly distant and soft breath sounds; there is no egophony or whispering pectoriloquy over this area or over the rest of the front of the right chest. On the left side in front the breath sounds are normal; save, perhaps, for a slight prolonged expiration. Behind on the right side inspiration is harsh, expiration prolonged; over the area of flatness numerous crackling rales of medium and fine character both on inspiration and expiration. Breath sounds here suppressed. On the left, with the exception of slight prolongation of expectoration there is nothing abnormal. No egophony and no whispering pectoriloquy.

Cardio-Vascular System: Save for a slight increase of the heart dulness there is nothing abnormal in this system.

Digestive System: No difficulty in swallowing, keeps his food down for hours, vomiting off and on, the abdomen is normal on physical examination save for some diffuse epigastric resistance.

Nervous System: The nervous system is normal.

Genito-Urinary System: The genito-urinary system is normal.

Locomotor and Integumentary System: Pallor, emaciation, asthenia, large bones, normal spine.

Blood Examination:

Red blood cells....................3,984,000
White blood cells..............   9,100
Hæmoglobin....................   70%

The differential count shows:

Polymorphonuclears.............   54.6%
Basophiles......................   2.3%
Eosinophiles....................   0.3%
Large lymphocytes..............   11.3%
Small lymphocytes..............   21.0%
Transitionals..................   4.7%
Unclassified...................   4.6%
Irritating forms...............   0.6%

300 cells counted.

The Wasserman reaction was negative. Repeated examination of 24-hour amounts of anti-formined sputum showed no tubercle bacilli.

On March 18th, patient vomited about 250 c.c. of undigested food; complained a good deal of headache and cough.

On March 23rd, bones were skiagraphed and showed diffuse enlargement, and a pale cortex which is thickened and smooth. The medullary canal is larger than normal, the epiphyses show odd lines in the laminary structure of the bone-ends, particularly the fibulæ.

On March 25th, an exploratory puncture of the right chest was done; no fluid was obtained and the needle entered with ease. The material examined showed a close resemblance to sputum, histologically and bacteriologically. It was poor in polymorphonuclears and lymphocytes, the predominating cells being endothelial. Budding yeast cells are numerous. Large Gram positive subtilis-like bacteria are present, also lancet-shaped diplococci which were Gram positive; there are abundant streptococci and some Gram negative diplococci.

On March 28th, a distinct tympanitic area was made out over the front of the right chest; there was, however, no amphoric breathing and no other signs of cavitation. The heart seemed somewhat pushed over to the left, and the general conclusions at the time led one to think that there might be fluid in the right chest close to the spine.

March 29th, patient was given a barium meal and fluoroscoped. There was a slight deviation of the œsophagus to the left at first, and at about the height of the 3rd rib the barium appeared to gather up to the right of the mid-sternal line in the pleural cavity in a big stomach-like pouch, while part of it went over to the left, leaving a narrow streak, and then entering another large low-placed pouch (apparently the stomach). The œsophagus was very wide at its beginning, and seemed to become wider until it joined the above-described first pouch, then it narrowed down, crossed from right to left, until it joined the stomach.

He is running a constant afternoon temperature ranging from 99° to 102°. Blood pressure is low—from 115 systolic to 110 systolic, the diastolic pressure running from 70 to 60.

The patient was discharged on April 17th with the following diagnosis: Diverticulum of œsophagus laying in lower portion of right pleural cavity, chronic bronchitis, and chronic poly-arthritis with chronic thickening of long bones of legs and arms. The patient was at home for some 16 days and remained approximately the same, with the exception that he had considerable pain in the ankles. He was again admitted to the hospital on May 4th with fever, pain in ankles, headache, shortness of breath, and joint pains. The patient's condition rapidly became worse, and without any apparent cause temperature began to rise attaining on the afternoon of May 9th 105°; pulse shot up to 108 and more. Respiration became more rapid, the physical signs showed little or no change from previous examinations, blood culture showed a saprophytic streptococcus, probably a terminal infection. Blood examination showed 3,840,000 red blood cells, 16,000 white blood cells, and 80% hæmoglobin. The urine was normal. Patient went rapidly down-hill. Pulse rapid, 150 and more, respirations 27–28. He died on May 11th, after having passed a fair night. For some hours before death he was very cyanosed, complained a great deal of left-sided severe pain and vomited several times a watery fluid.

The general impresssion at the time of death was that there seemed to be a marked and rapidly increasing respiratory and cardiac embarrassment. We consider the question whether, because of the frequent vomiting spells immediately before death, some food may not have got into his trachea and bronchi and given an added mechanical source of trouble; this source of trouble was discarded, as there seemed to be no increase in cough and no evidence of change in the chest on physical examination.

Post-Mortem Report

The post-mortem examination was done four hours after death.

The following notes are taken from the protocol: A. 78, '16.

Body of an adult male about 30 years of age, measures 165 cm. in length; good physique; nutrition poor; there is beginning *rigor mortis* and some post-mortem lividity in the dependent parts. Skin is soft, white and elastic; there is no rash and no œdema. Conjunctivæ are clear and pupils measure 4 mm. each. The neck is long and thin, thyroid cartilage and gland somewhat prominent. Posterior cervical glands are somewhat enlarged. Muscles generally are wasted, chest is long and rounded, abdomen is flat and genitalia are normal. Slight clubbing of nails.

On opening the abdomen the liver is low, reaching down below the umbilicus. The dome of the diaphragm is at the 7th rib on both sides. The upper border of the liver is just above the costal margin. Bowels are distended. No ascites. The chest organs and abdominal viscera were removed *en masse*.

The examination of the organs as removed shows a large mass involving the cardiac end of the stomach and extending to the right through the diaphragm, and involving the greater part of the œsophagus. The upper œsophagus is dilated into a huge sac of somewhat the shape of a stomach and lies behind the lower lobe of the right lung. At the level of the 1st dorsal vertebra the œsophagus is 13.5 cm. in circumference and the wall is 0.5 mm. thick.

The lungs show no evidence anywhere of recent or healed tuberculosis. There is a bilateral old fibroid pleuritis. Some œdema and passive congestion of dependent parts of lungs.

The heart is small, the pericardium, endocardium and myocardium are normal.

The kidneys are large and show evidences of passive congestion, otherwise they are quite normal.

The liver is moderately congested.

The gall bladder is normal.

The intestines are normal. The bladder and genital organs are healthy. The adrenals are normal. There is no evidence anywhere of metastatic nodules of new growth. There was no evidence of new growth in the sternum, ribs or vertebræ. The long bones and brain were not examined.

A careful examination of the œsophagus reveals the following important facts:

The organ ran a distinctly abnormal course—beginning with the central position at the entrance into the thorax, it coursed to the right, gradually crossing the bodies of the spine, and then occupied a position to the right of the spine until the main tumour mass was reached, the greater part of which was also to the right of the spinal column.

The main outline of the organ was as follows:

It was hugely distended, and this distension began practically at the origin of the organ. At the upper border of the sternum, the œsophagus measured 15 cm. in circumference. The width gradually increased in size until it reached about the level of the 8th dorsal vertebra, where it measured approximately 16.6 cm. in circumference. Below this wide area the œsophagus seemed to constrict abruptly, this constriction being due at first to a marked hypertrophic condition of the muscle layer, which gradually led into a huge tumour almost the size of the head of an average child of 10 years. There is, however, a marked distinction in the gross between the œsophagus muscle and the tumour. From the beginning of the tumour to its entrance into the stomach the œsophagus measures 20 cm. in length, and this entire portion of the organ is enveloped in a huge, firm, partly lobulated, poorly vascularized, pale fibro-muscular tumour.

The tumour is somewhat irregularly ovoid in outline, and occupies the following anatomical position:

It lies obliquely transverse in the chest, having its upper portion well to the right of the midline, then runs slightly obliquely to the left downwards and forwards, twisting the diaphragm upwards and to the left. On the right it is covered

by the lung in front, and below the diaphragm by the left lobe of the liver. Behind it is in close approximation with the vertebræ and chest wall. The heart lies above and to the left touching on the tumour; below it rests on the diaphragm and liver. Two-thirds of the tumour is above the diaphragm and one-third below. The weight of the œsophagus, tumour, and stomach (the latter organ being of normal size) was 2540 grm. A gross section through the tumour into the œsophagus shows that the tumour wall encircles the lumen of the organ, and that it has given the œsophagus a somewhat sinuous curve. The markedly distended œsophagus, 'immediately above the tumour, as already described, was so twisted to the right and so distended that it had the appearance and outline of a stomach. The œsophagus above the tumour was filled with a thick, gruelly substance, reminding one of mascerated wet filter paper. These contents entirely filled the organ. The œsophagus in its course through the tumour was comparatively empty, but there was no obstruction. In addition to the marked distension of the œsophagus above the tumour there was also a remarkable degree of hypertrophy of the muscle, which measured at the upper border of the sternum approximately ½ cm. in thickness and increased gradually, until just at the point where it joined the tumour it measured 1.7 cm. in thickness. The serosa is thick, fibrous, and very adherent to the diaphragm, but not adherent to the pleura or pericardium. The point where the tumour joins the stomach is interesting, since it accurately outlines the digitations of the œsophageal muscle as it joins the stomach. The stomach itself is normal, showing no thickness of its walls even at the point of junction with the tumour.

The mucous membrane of the œsophagus is thick, save where it passes through the tumour, where it is thin. It is smooth and pale.

MICROSCOPICAL EXAMINATION

The microscopic slides demonstrate clearly the benign leiomyomatous character of the tumour: Sections taken from the thickened œsophageal wall just above the tumour mass

show on the surface a thin layer of squamous epithelium lying on a thickened fibrous connective tissue layer. The remainder of the section is made up of thick, hypertrophied layers of smooth muscle tissue, and shows extremely well the tremendous thickening of the œsophageal wall due to this increased musculature. The sections from various parts of the tumour show a picture closely resembling that of a typical fibromyoma of the uterus, made up of numerous coils of thick layers of mature, well developed smooth muscle intermingled here and there with connective tissue strands. The tumour is poorly vascularized.

Conclusion

The following points appear of interest:

A. *Clinically:*

1st. Cough and expectoration with shortness of breath, particularly troublesome in the winter, were outstanding features practically since the age of five.

2nd. The constant absence of tubercle bacilli from the sputum, even when 24-hour amounts were treated with anti-formin and slides were carefully searched. (This, of course, was from the start against the diagnosis of tuberculosis.)

3rd. The prolonged history of vomiting of moderate quantities of food late after meals, which frequently showed a poor state of digestion.

B. *Anatomically:*

1st. The tremendous size of the tumour, which, in so far as our search of the literature is concerned, makes it practically a unique case.

2nd. The relatively good condition of all the other organs in the body, but the rather sudden death, would tend to support the idea that death was due to a combination of circumstances, the most important of which were the great pressure exerted by the hugely distended œsophagus and tumour mass on the important nerves of the thorax and a compression of the trachea and the main bloodvessels which leave and enter the thorax.

3rd. There was little or no mechanical interference with the heart action by the œsophageal tumour, as the heart was quite free in its movements in all directions except to the right.

4th. It seems, from the size and histological picture and clinical history, reasonable to suppose that the growth of the tumour was extremely slow and probably dated from childhood or, possibly, still earlier.

The following letters are a key to the different organs in the diagrams; the relations and relative sizes of the organs have been very well reproduced by the artist and need no other explanation:

L. Lungs.   S. Stomach.   O. Œsophagus.
D. Diaphragm.   T. Tumour.   K. Kidney.
H. Liver.   C. Heart.   A. Aorta.
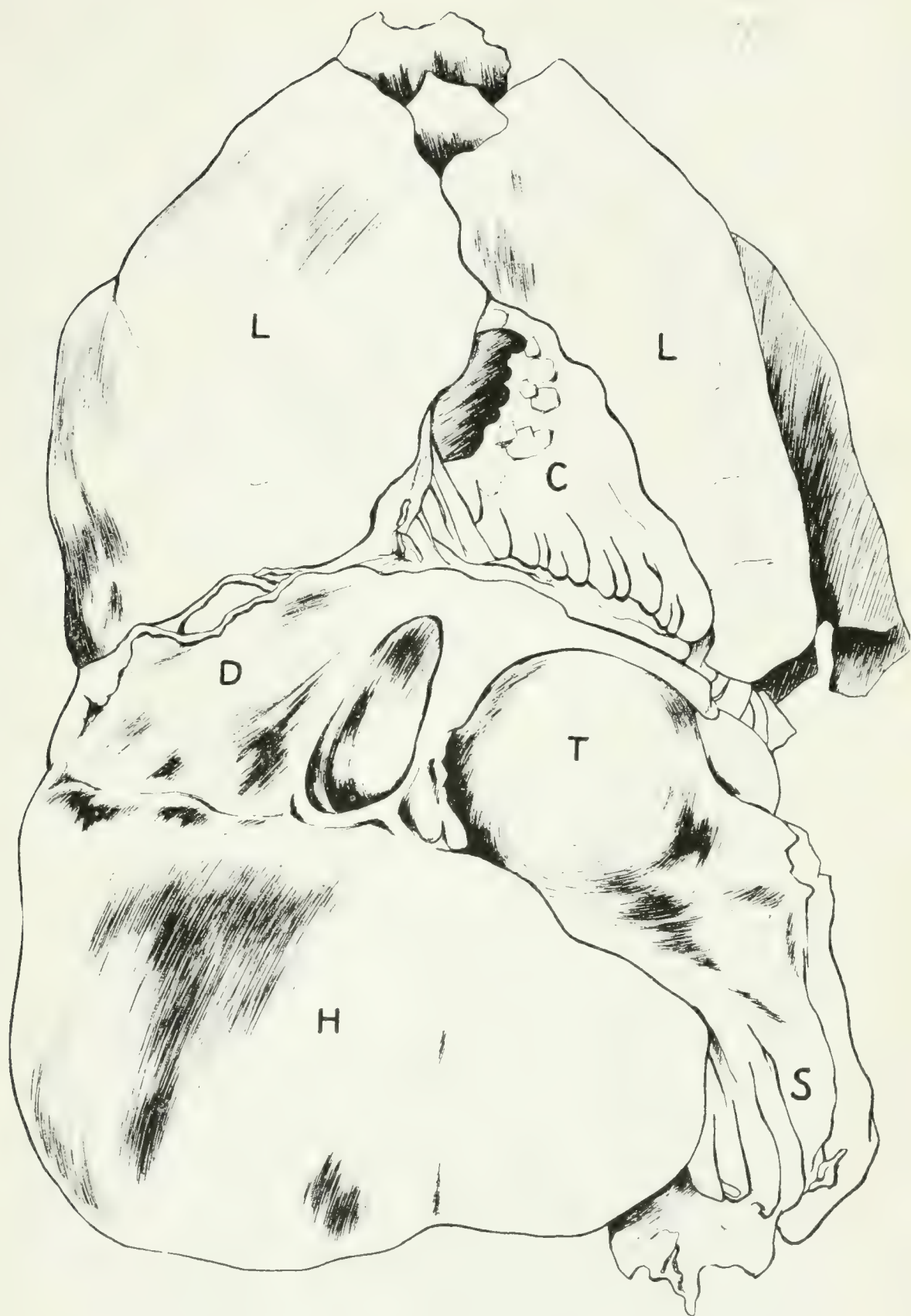
FIG. 1.—Anterior view.

Fig. 2—Posterior view

FIG. 3.—Anterior view. (Right lower lobe of lung pulled aside leaving tumour exposed.)

FIG. 4.—Posterior view. (Lungs dissected away and left lobe of liver pulled over to right, exposing whole outline of tumour. Stomach opened.)

FIG. 5.—The œsophagus is laid open and shows the great width of the upper œsophagus and the exact outlines of the tumour.

ON SOME HEPATIC ABSCESSES,
A CLINICAL STUDY

By Emerson C. Smith

(From the medical service of Professor W. F. Hamilton)

Clinical and pathological investigations, even up to recent times, have failed to clearly explain the origin and nature of many hepatic abscesses. There is no doubt, however, that infection in most cases arises from the alimentary canal, but frequently evidence is quite lacking. The fact, too, that in so many instances cultures from these abscesses remain sterile, renders the source of infection still more obscure. In four of our series no growths were obtained from the pus. The findings, too, at autopsy reveal not uncommonly that abscesses may exist in the liver for a very long time without manifesting clinical symptoms; that, moreover, they may even heal and show nothing but a chronic scarred condition after death.

That latent infection may exist is also obvious, and, as is shown in one of our series, a recurrence may occur after many years of old focal disease. Indeed, it may readily be a matter of surprise that liver abscess is not a much more common event, considering the frequency of focal disease in all general infections.

Experience shows, too, that the development of these abscesses may occur over a period of many months, perhaps even years, and that after an acute onset the condition may subside and remain much as does a so-called cold abscess, in a state of quiescence, or slow progress, the infecting organism ceasing to have sufficient virulence to initiate further development. From the clinical standpoint it is of interest to note the variety of clinical symptoms, frequently their entire absence.

The pain which, too, is sometimes lacking even late in the disease, shows in our own cases two sites of selection, the

right epigastrium and the back. It seemed as a rule to bear no relation to the ingestion of food. Noteworthy, too, are the long periods of remission from pain which has been observed.

Fever was a variable feature, absent in some cases, slight in others, while on one occasion it was of a virulent septic character.

Chills and sweating are by no means essential features of the clinical picture, and seem to occur only where there are other signs of severe sepsis. The pulse is not necessarily accelerated.

As a rule digestive disturbances are absent. It is noteworthy, too, that abdominal distension, rigidity and tenderness may be quite inconspicuous, if not entirely wanting. Loss of weight was a feature common to all our cases, beginning sometimes before the local symptoms developed (due to some other primary cause), or forming part of the septic picture. Leucocytosis, however, was the usual finding in the blood.

The bacteriological findings often afford no clue to the origin of the focal disease, and, as already stated, in four of our series the cultures from the pus were sterile.

CASE 1. *Liver Abscess and Gallstones. Operation. Recovery.*

W. C., æt. 53. White. Clerk.

This patient had complained of slight pain over the region of the navel six months previously, gradually increasing in severity up to three months ago. The pain later on radiated to each side of the spine, where it remained up till his admission to hospital two months later. It was described as of a tearing nature, and constricting, getting worse at night for several hours, and having no relation to food. There were no nausea, vomiting, jaundice, melena, nor constipation.

After five weeks of perfect health the pain recurred, and loss of weight was noted for the first time.

Five and a half months after his initial symptoms (which may have been due to his cholelithiasis) he developed more sudden pain of a severe stabbing nature, still in the region of

the navel and coursing to the back, especially on the right side, and accompanied by dyspnœa. There was neither any chill, sweating or fever, and the pain persisted for two weeks before he entered the hospital.

The Personal History contained only two facts of importance, viz.: malaria (8 years previously) and alcoholism.

Examination revealed a thin, pale, sallow man with no cyanosis, nor pain at the time. Temperature 100. Pulse 72. Respirations 20.

The Circulatory System was normal except for a leucocytosis of 20,600, and the hæmoglobin was 55%.

In the *Respiratory System* it was noteworthy that the right lung descended 2 cm. lower than the left.

Digestive System. There was some pyorrhœa. The abdomen was full and tympanitic throughout, and the right kidney was movable.

The liver was smooth and tender, and extended 5 cm. below the costal margin in the mid-line. McBurney's point was tender and rigid.

The rectum was negative, as were the stools. Hydrobilirubin was abundant.

The Genito-Urinary System was normal. There was no bile in the urine.

The *Diagnosis* of liver abscess was made, and operation performed.

The appendix was normal and there was no sign of obstruction.

The right lobe of the liver was filled in its upper part by a fluctuating and œdematous mass, and a few gallstones were found in the bladder.

A portion of the 7th rib and cartilage were resected.

The two pleural surfaces were stitched together. A needle was then inserted through the pleura into the mass, and 3 pints of brownish fluid (not thick pus) were removed. The opening was enlarged, and suitable drainage afforded. The material consisted chiefly of a moderate number of leucocytes and broken-down liver cells and detritus.

No amœba were found.   Cultures remained sterile. Recovery.

Where the primary focus was, remains in doubt.   The gall-bladder, apart from the presence of stones, showed no evidence of the same infection as existed in the liver.   Nevertheless, no other origin for the hepatic abscess was found, even after the most careful examination at operation.   The patient subsequently returned home, and although the acute condition subsided he never recovered strength sufficiently to perform his duties.

Some months later signs of œsophageal cancer developed, and within a year after his exit from hospital he died.

Doubtless in this case a slowly growing epithelioma was the source of the hepatic abscess, the acute infection masking the original disease.

CASE 2.   *Liver Abscess with Perforation.*

D., æt. 27.   Russian.

This patient had complained, but a few weeks before admission, of sudden severe epigastric pain radiating to both sides of the chest.   It was increased on breathing and had no relation to food.   After one week it subsided till a fortnight passed, when a second attack occurred, worse than before, and located more on the right upper abdomen.   After several days the symptoms disappeared, only to recur in a fortnight with equal severity.

There had been weakness, loss of weight, and general malaise, but the bowels had been regular, and only on one occasion had there been an abnormal stool which was very dark in colour (? medication).

There was no vomiting.   Jaundice was absent, and at no time during the course of the illness had there been fever or chills.

The Personal History was quite good.

Examination revealed a man without pain and seemingly not acutely ill.   The epigastrium, however, was tender, especially at the costal margin in the right nipple line, and the

abdomen was rigid in its upper half. There was no distension. The region of the appendix was normal.

The Circulatory and Respiratory Systems were normal, and there was no bile in the urine.

The stools, however, showed abundance of occult blood.

The diagnosis could not be made with certainty, but the tenderness and other symptoms in the neighbourhood of the gall-bladder suggested a possible cholecystitis and hepatic abscess.

Operation was performed (Dr. Garrow), and disclosed a large liver abscess, the upper portion of which lay close to the diaphragm, to which it was adherent, and through which it was drained. At the lower portion it was found to have perforated into the region between the stomach and liver, where it remained localized.

The pus from the abscess showed detritus and fluid with remarkably few cellular elements other than red blood cells. No parasites were found and cultures remained sterile. The primary focus could not be determined, nor was the nature of the infection evident.

CASE 3. W. K., æt. 46. Irish.

Entered the hospital in May complaining of pain in the epigastrium, nausea, vomiting, weakness and loss of flesh.

The *Personal History* was negative.

There was a Family History of tuberculosis.

The patient stated that he had had attacks of acute abdominal pain for 20 years; at first weekly, then less often. During recent years the attacks would occur not more than once or twice annually. The pain, beginning in the epigastrium, was of a tearing character, radiating all over the abdomen and liver, also to the scapula, and with each paroxysm there was nausea and sometimes vomiting. The duration of these attacks was rarely more than 24 hours, and each one ended abruptly. Jaundice had occurred once only (7 years ago), during an attack.

The present attack, however, had begun six weeks before admission, and as usual lasted one day. The patient was then

comfortable for a week, when the pain became more widespread and accompanied by so much distension and rigidity as to lead to the diagnosis of acute peritonitis. The symptoms, however, subsided, and the patient was comfortable for three weeks, with only occasional sharp pains. There were no rigors, and fever was not observed.

Synopsis of the status præsens. A large mass was found in the epigastrium filling that area down to the umbilicus. It was smooth, firm and tender, apparently a much swollen liver. The region of the appendix was normal.

The X-ray examination showed the stomach pushed much to the left, but there was no other abnormality shown by this means.

The *Respiratory System* was practically normal, as was also the *Circulatory System*, except that the leucocytes were 20,000 in number.

A diagnosis of Hepatic Abscess was made, and two days after admission Dr. Garrow operated. A localized abscess between the liver and stomach was found, but no primary focus whatever was detected.

Progressive weakness and prostration followed the operation, and the patient went home and died shortly afterwards.

An autopsy was not obtained.

No record was found of the bacteriological findings.

CASE 4. R., æt. 53. Russian.

Entered hospital in October complaining of pain in the right side.

The Personal History revealed an attack of typhoid eight years ago, but was otherwise unimportant.

Two weeks prior to admission, the patient, without previous malaise, had a sudden rigour while at work and took to his bed. Headache and cough immediately followed, and a diagnosis of influenza was made. In a week the dull pain in the right side began; it was constant, increased on respiration and was relieved by lying on the right side. The temperature was then 99; pulse 86; respirations 36; and there was profuse sweating. During this time the patient only vomited twice,

but constantly complained of tenderness in the upper abdomen.
On admission there was icterus, the temperature was septic,
and the leucocytes were 24,600. There were no chills. The
gall-bladder region was painful and tender, with localized
rigidity. There was tympany on percussion. The liver edge
was merely palpable, but the area of hepatic dulness in the
mid-clavicular line was 7 inches.

Examination of the chest shewed marked pain on deep
inspiration.

Emphysema was present. The lower areas of the lungs
were almost immobile. There was some bulging of the right
side, and diminished focal fremitus at the bases. There was,
however, no dulness or evidence of friction.

The fluoroscopic examination of the chest shewed the right
diaphragm somewhat pushed upwards, fixed and immobile.

The urine contained a trace of bile.

Diagnosis. A diagnosis of Hepatic Abscess was made,
which was confirmed at the operation by Dr. Keenan. The
abscess was drained. Examination of the pus, as well as of
the viscera, revealed no cause for the abscess. Cultures were
sterile.

Patient made an uninterrupted recovery.

CASE 5. S. Roumanian.

Entered the hospital in September. Complained of pain
in the right upper abdomen, dyspnœa, fever, malaise, weakness
and loss of weight.

The Personal History was negative.

The patient had been poorly for six months with weakness,
loss of weight and apathy. Apart from that, there were no
other symptoms until six weeks prior to admission, when the
above-mentioned complaints developed.

After early general malaise the headaches became worse,
and cramp-like pains in the abdomen developed, with marked
constipation. There was no nausea or vomiting. Suddenly
four days before entrance, the symptoms became much worse.
There was profuse diarrhœa and the patient reached a state
bordering on collapse. On admission his temperature was 104;

pulse 112; respirations 28. He was markedly anæmic and the leucocytes were 18,000. The abdomen was distended and doughy, and the right hypochondrium tender. The spleen was enlarged, and slight tenderness could be felt in the right upper quadrant, but with no rigidity. The liver was not palpable, but the levulose test showed hepatic insufficiency.

Examination of the chest shewed lagging of the right side below, and dulness on percussion. From the angle of the scapula downwards the signs were those of fluid and paracentesis. Ten ounces of bloody fluid were removed from the right pleura.

Bile was present in the urine, as were also albumen and casts. Many pus cells were also found in the sediment.

Operation was performed by Dr. Archibald, who exposed the liver after removing thick green pus by the syringe. Two ribs were resected, and the liver abscess drained. Cultures showed coli bacilli and streptococci.

Death occurred a few days afterwards and the autopsy showed a multiple chronic pyococcic liver abscess, without any signs of perforation.

The chronic character of the abscess was particularly worthy of note.

No origin of the abscess could be found.

CASE 6. W., æt. 59. German.
Entered the hospital in June.

Personal History. In 1914 he had been in Mexico, and later on in the same year came to Canada. In April 1914 he infected his hand, and was obliged to absent himself from work for six weeks. For the following three weeks he was well, and then showed signs of general malaise, weakness, fatigue and pain in the right side. The pain remained off and on, of varying duration for some months. For four months, at the end of 1914, he was well, but early in 1915 the pain had again become severe and was referred more to the back. They were paroxysmal in character, occurring every three or four days, more often at night, and progressively more severe and more

frequent in the occurrence. After this, there were chills, sweats and much loss of weight.

On admission to the hospital there was constant pain of a dull nature over the right costal margin, just outside the region of the gall-bladder, and the area was tender to the touch. The temperature was of a markedly septic type and accompanied by chills; the pulse was 90.

There was no jaundice, and the stools and urine were normal.

Examination of the abdomen showed the liver palpable and enlarged in both its right and left lobes. The blood was normal.

Operation was performed, and a solitary liver abscess of the right lobe was found and drained.

Death followed shortly afterwards, and the autopsy revealed an encapsulated healed abscess, adjacent to a more recent abscess alongside.

There was general peritonitis.

Cultures from the pus were sterile.

In the lungs there was tuberculosis with multiple abscess formation, and general sepsis throughout the body.

It seems possible to associate the old hepatic abscess in this case with the history of infection in the finger, though to what extent the tuberculosis with *its* secondary infections may be responsible it is hard to state.

TABULATION OF CASES

	I	II	III	IV	V	VI
1. Age	53	27	46	53		59
2. Duration	6 Months	1 month	Long, 20 yrs.	2 weeks	6 mos. & 6 wks.	6 mos. or +
3. Alcohol	+	o	o	o	o	—
Malaria	+	o	o	o	o	o
Typhoid	o	o	o	8 yrs. before	o	o
4. Rel. to food	o	o	o	—	—	o
Nausea	o	o	o	twice	—	o
Vomiting	o	o	o	+	—	o
Jaundice	o	o	o	+	—	o
Dyspnœa	ı	ı	—	—	ı	—
Pain	Navel + to spine	Epigastric ++ Sudden to sides Remissions	Epigastric ++ Radiates all over and to back Remissions	Right side +	R.V.Q. Cramp general	R.V.Q. and to back Intermittent
5. Loss of weight	ı	ı	ı	—	ı	++
6. Sweats	o	o	o	+	ı	+
Feverish	o	N	—	Influenza	—	ı
Temperature	100		—	99	++	++
Chills	o		o	Onset	—	+

TABULATION OF CASES—Continued

	I	II	III	IV	V	VI
7. Bile in urine	o	o o	o o	+	+	o
Stools						o
8. Leucocytes	+	?	+	+	+	o
9. Rigidity	o	-	-		o	++
Distension	+	o		++	+	
Liver+	-		-	-	o	-
Liver tender	-	-	-		-	
10. Appendix	-	o o	o o	o o	o o	o o
Appendix found	O.K.					
11. Stools	o	o	o	o	o	o
12. Bact. findings	o	o		o	o	o
Parasitic "	o	o		o	o	o
Pus	Brown fluid	Debris	-	-	++	?
13. Result	R		D	R	Chronic multiple abscesses	Acute or chronic
14. Primary focus	? Gall bladder	o	o	o	o	Tbc o sepsis.

GASTRITIS GRANULOMATOSA FIBROPLASTICA. (LINITIS PLASTICA. FIBROMATOSIS OF THE STOMACH. CIRRHOSIS VENTRICULI. LEATHER-BOTTLE STOMACH)

By George E. Armstrong

(From the surgical service)

At the meeting of the Canadian Medical Association held in St. John, N.B., in July 1914, I presented a short report of three cases of Fibromatosis of the Stomach that I had operated on in the Royal Victoria Hospital together with one in the service of my colleague, Dr. Garrow. Since then I have had two other cases. I have now, therefore, five cases that I have operated on for consideration. These cases have been studied with considerable interest because of their rarity and because of the many interesting and as yet unanswered questions regarding the pathological changes, the etiology and prognosis, as well as the clinical history, diagnosis and treatment of this condition. In each of the five cases I removed a considerable portion of the stomach—all that seemed to be involved—as well as a small part of the duodenum, closing the openings in the stomach and duodenum, and finally performing a posterior gastro-enterostomy. Sufficient tissue has thus been made available for examination in each case. It is perhaps not altogether unfortunate that, owing to changes in the hospital staff, two distinguished pathologists have contributed their bit towards the classification of the obscure questions pertaining to Leather-bottle Stomach.

The distinctive feature is a definite, and in some cases an extreme, hypertrophy of the submucous layer of the stomach. Brinton found it in some cases ten to twenty times its normal thickness. The hypertrophy of the sub-mucosa occasionally occurs in patches or plaques but is usually diffuse, beginning

at the pylorus and extending along the antrum. It may
involve the fundus, and the whole stomach be so thickened
and contracted that its total capacity is reduced to one or two
ounces. While the changes in the walls of the stomach are
found chiefly in the sub-mucosa, the muscularis and serosa may
be altered to a lesser degree. The changes in the muscular
coat consist in a marked hypertrophy of the circular fibres
only. The longitudinal fibres do not take part in this change.
The hypertrophy of the circular fibres may be regarded as
compensatory, and in response to the greater effort required
to force the stomach contents through the narrowed pylorus.
It is absent when the pylorus is not involved. The circular layer
is not only hypertrophied—it is also segmented by partitions
or septa of white fibrous tissue continuous with the fibrillated
tissue of the sub-mucosa. Thomson and Graham, who made
this observation, regard it as a characteristic feature of fibro-
matosis, for while the hypertrophy of the circular muscular
coat may be as marked in pyloric stenosis due to cancer, the
segmentation is not present to the same degree. Dilatation
of the stomach in this disease is not common. The hyper-
trophy of the sub-mucous coat generally ends abruptly at the
pyloric ring.

   According to W. H. Welch, observations on this condition
date back to the seventeenth and eighteenth centuries, perhaps
even earlier. During the nineteenth century improved meth-
ods of study and examination of specimens gave a fresh im-
petus to the investigations into the nature of this obscure
condition. Among those who contributed may be mentioned
Butzen, Pohl, Andral, Broca, Cruveilhier, Brinton, Tilger,
von Sury, Curtis and Krompecher. It would seem that the
condition had been considered benign until Rokitansky in 1859
suggested that sub-mucous hypertrophies of the stomach be-
longed to the group of fibroid cancers. From that date up to
the present observers have been divided, one group regarding
the condition as malignant and the other as benign. Among
recent writers the question has been very judiciously considered
from the medical side by Martin in Osler's *Modern Medicine*

and from the surgical side by Thomson and Graham in the Transactions of the American Surgical Ass., Vol. xxxi.

In addition to the six cases observed at the Royal Victoria Hospital must be mentioned one occurring in the practice of the late Dr. Drake, which was seen by Osler and described in his *Principles and Practice of Medicine*. In this case the stomach was no bigger than a cucumber, and the cæcum and part of the ascending colon showed the same thickening. A careful study of this case has shown it to be of the malignant type. At least six cases have been observed in Montreal of the benign type.

When the stomach is exposed the limitations of the disease are well defined. In cases of long duration the walls are very hard to the touch. The induration extends from the pylorus towards the cardiac end, where it shades off measurably, i.e., it does not present the same abrupt ending observed at the pyloric end. In one of my cases, evidently of shorter duration than the others, the thickening of the coat was very marked, but the density was less than usual. In appearance the coats were more glistening and waxy looking.

In one case there was a small plaque, the size of a small soft-shell almond, on the upper end of the duodenum. The same condition of thickened sub-mucosa found in the stomach has been found in both the small and large intestine, though much less frequently.

In the diffuse form, which is the more common type, the appearance of the stomach at the operating table is quite different from ordinary carcinoma, but resembles the chronic scirrhus carcinoma of the stomach so closely that the one cannot be distinguished from the other. It has not the puckered, uneven, nodular appearance of common cancer. It is smooth, pale in colour and involves the whole circumference of that part of the stomach affected. Nor does it at all resemble the contracted area seen over an ulcer, nor the thickened tumour-like enlargement occasionally seen in association with ulcer.

In early cases the stomach is movable and not adherent to the pancreas. In more advanced cases of longer standing

the serosa is thickened, and may be so bound down by adhesions that neither resection or even a gastro-enterostomy is possible.

It is generally conceded, and this is an important point, that at the operating table the experienced surgeon is unable to determine definitely whether the condition is benign or malignant.

The lymph nodes along the lesser and greater curvature are enlarged in the more chronic cases. They are not numerous. They preserve more nearly their normal shape and they are not as hard as in malignant disease, but the differences are not sufficiently clear and definite to justify a conclusion.

The difficulty, in fact the impossibility, of the operating surgeon deciding at the operating table whether the case is benign or malignant is more fully appreciated when an examination is made of the excised tissues. It is held by some observers to-day that all cases of Cirrhosis Ventriculi are malignant, and that if a sufficient number of slides are examined that cancer cells will be found. Against this view two statements may be made. First, that patients whose stomachs have been partially resected have lived for years without evidence of recurrence; others have died years after their operations and no evidence of malignancy found at autopsy; and others, when the extensive involvement of the stomach and the numerous dense adhesions have permitted only a gastro-enterostomy, or in one or two cases a jejunostomy without removal of the diseased area, have lived for years afterwards without developing a condition recognized as malignant. Secondly, that capable pathologists have carefully examined the removed portions in numreous instances without finding evidence of malignancy. I am inclined to agree with Oertel, Gruner, and other pathologists that there is a definite entity, call it what we may, whose characteristics are thickening and induration of the sub-mucous layer of the stomach with atrophy of the glands, and generally associated with hypertrophy and segmentation of the circular muscle fibres of the stomach and often moderate thickening of the serosa; and that the condition is benign.

What relation does this disease bear towards scirrhus carcinoma of the stomach ? Some may reply, none. I think most pathologists now teach that benign conditions do not change their character and become malignant. Many clinicians believe that cancer is always preceded by some deviation from the normal of the tissue in which it takes origin. So far as I know Keen's statement that there was no case of cancer of the skin on record that had not started in some injury or other lesion of the skin has never been challenged. It appears to be reasonable to think that the changes that take place in the sub-mucous layer of the stomach in fibromatosis may favour the development of cancer in much the same way that benign tumours are believed sometimes to favour the growth of a cancer in the breast.

Gruner, after a careful study of the tissue removed in my first three cases, reported that he found no evidence of malignancy. He also expressed the opinion that there might be a tendency to terminate in scirrhous carcinoma from a constricting action upon the bases of the gastric glands. Another point of interest in this question of malignancy in association with fibromatosis is the constant or almost constant association of the disease with an ulcer of the mucous membrane of the antrum, usually situated close to the canal of Jonnesco or at any rate near the pylorus. These ulcers are often surfecial and in some cases not easily found. In other cases they are deep, punched out, with hard base and indurated edges. Cancerous growths have been found beginning in the borders of these ulcers. Apparently, then, there are several associated conditions that in untreated cases might contribute to the starting of a malignant growth.

When the resected portion of the stomach is opened the mucous membrane is generally found folded up and sometimes thickened. It thus contributes to the narrowing of the pylorus. The tissues are unlike scar tissue in that the layers preserve their identity and are not smelted together.

To the report of my first three cases published in the

Journal of the Canadian Medical Association, September 1914, I will add a very brief summary of my last two.

Female, æt. 36. Married. Complains of epigastric pain and distress. Five years ago I removed the left breast for carcinoma. Since then has been in good health until 6 or 7 months ago. No sign of recurrence. The stomach symptoms began 6 or 7 months ago, and consist of pain coming on ten minutes to an hour after food and latterly generally relieved by vomiting, although it sometimes passes away gradually. Also complains of a burning sensation in the mouth, and complains of lack of energy. Looks pale. Family history negative. No history of any stomach trouble previous to present illness. No mass to be felt. A little epigastric tenderness. No constipation. The liver showed a definite cirrhosis. Urine normal. R.B.C. 3,000,000. W.B.C. 13,000. Hæ. 55%. No gastric stasis. Free H.c.l. 18%. Total acidity 36%. No lactic acid. A trace of blood. No pus; sarcinæ or Oppler Boas. Rectal examination negative. No hæmorrhoids. Stools normal in colour and contour. No blood, pus, or ova. Respiratory and cardiac systems normal. No pathological reflexes. No enlarged palpable lymph nodes. No evidence of tubercle or lues.

The X-ray examination showed a very definite filling defect in the pyloric end of the stomach. The clinical and X-ray diagnosis was carcinoma of the stomach. When the stomach was uncovered the right third of the viscus presented the typical appearance of an early condition of "leather:bottle stomach." Two or three enlarged lymph nodes presented no evidence of malignancy on frozen sections. The indurated portion of the stomach was resected and a posterior gastroenterostomy performed, followed by a remarkably rapid and satisfactory convalescence.

Dr. Oertel's report on excised portion of the stomach is the following: "Specimen represents the pyloric end of the stomach and measures 8 cm. in length. The wall is 1⅝ cm. in thickness at its thickest portion, this thickening being particularly at the expense of the sub-mucous coat. The mucous

membrane showed numerous but superficial ulcerations, but these ulcerations did not extend into the deeper tissues. The thickened wall was firm, but not of the stony hardness frequently encountered in scirrhous cancers. The serous coat was smooth and pinkish. Microscopic examination of various parts showed essentially the following lesions: The submucous-coat is diffusely and densely infiltrated by lymphoid cells. This infiltration obliterates in parts the boundary of the mucosa and sub-mucosa and becomes continuous with a similar infiltration of the lower parts of the mucous membrane, in which are also involved the lymphatic follicles by hyperplasia. Thus mucosa and sub-mucosa are gradually overgrown by lymphoid cells which rest and extend within a thin reticular tissue. In other and apparently more recently extended parts the lesion presents itself in marked perivascular lymphoid cell infiltrations confined to the deeper portions of the sub-mucosa, while its upper part and the mucous membrane appear intact. The glandular elements of the mucous membrane do not seem to play any active part in the process at all, but where they have become overgrown by lymphoid cells and probably also have been damaged by nutritive changes, local necrosis ensues and the mucous membrane shows rather superficial ulcerations. If one now examines parts of what appear to be the well-established and older processes, the lesion seems to play in, and progress, particularly in the sub-mucosa. In this are also found definite arterial changes. These in the larger vessels are an endarteritis obliterans associated with thrombus formation; and even in the smaller vessels endothelial proliferation leading to thickening of their walls is evident. In these older foci there appears an irregular, rather unhealthy, fibroplastic proliferation displaying a tendency to kariorrhexis. In the deeper portions of the sub-mucosa there has thus been produced a mature, thick and hyaline but unhealthy fibrous tissue. While in the upper portions of the sub-mucosa the tissue shows greater uniformity in lymphoid cells, the type becomes polymorphous in the deeper and apparently more mature parts. There are

lymphoid and epithelioid and occasionally very definite giant cells, some of which may be due to the fusion of thrombosed capillaries. The lesion stops rather abruptly at the muscular coat. This remains unchanged and undergoes moderate hypertrophy. The serous coat is moderately thickened by fibrous tissue, well separated from the muscular coat, and shows some perivascular lymphoid infiltrations with thickening of its blood-vessels.

CASE 2. Admitted 18th January, 1915.

Male, æt. 57. Married. Complains of epigastric pain and distress, and vomiting and loss of weight.

He was first admitted to the Royal Victoria Hospital in April 1914. A diagnosis of gastric carcinoma was made at that time, but he refused operation and was discharged. On readmission, January 1915, he says that his stomach trouble began fifteen months ago. At first he had only a feeling of distress, but latterly he has vomited two or three times a week, generally in the evening, bringing up a considerable quantity, more he thinks than taken at the immediately preceding meal. The vomiting relieves his pain and distress. Never saw blood in vomitus. Free Hcl. 20. Total acidity 40, lactic ac. present. No Oppler Boas bacilli. A few red blood cells. He is a small, poorly nourished man, with a rather cachectic look. No glandular enlargement. Reflexes active and normal. Cardio-vascular system negative. The abdomen is flat; moves freely during respiration. A mass, apparently the size of an orange, is seen to move up and down with the movements of the diaphragm. It is situated in the epigastum a little to the right of the median line. It suggests a growth in the pylorus. Kidneys and spleen are not palpable. There is no visible peristalsis and no evidence of free fluid. Rectal examination negative. The epigastric pain that the patient complains of is a dull, steady ache, and bears little relation to food. Complains of burning sensations and eructations of sour, bitter matter. Has lost 34 lbs. in weight. R.B.C. 4,000,000. W. 5,600. Hæmoglobin 71%. Liver normal. The thickened area was removed, the ends of the stomach and duodenum

closed and a posterior gastro-enterostomy performed. The patient made a smooth and uneventful recovery. Only 2 or 3 glands found enlarged, and these were removed.

Dr. Oertel reports: "Microscopically, the coats of the stomach, with the exception of the serosa, are all thickened, but well differentiated. The mucous membrane is well defined from the underlying extremely thick and fibrous sub-mucous tissue, and sits straight upon it. Only isolated thin streaks of fibroblastic and lymphoid cells are seen to occasionally extend from one into the other. Where the mucous membrane over these thickened areas is best preserved it shows hypertrophy of the mucosa with accentuation of its villous arrangement and large, well formed glands with delicate basement membrane and high cylindrical epithelium, separated by cellular septa of tunica propria. These areas interchange with others in which the superficial portions of the mucous membrane become necrotic, and are deeply infiltrated by lymphocytes which overgrow the glands and tunica propria and lead to their loss. The deeper parts of the mucous membrane show throughout marked dilatation of bloodvessels and lymphatics, which are frequently filled by coagulated lymph. This dilatation assumes occasionally the dimensions of ectasy. The massive lymphoid cell infiltration of the deeper portions of the mucous membrane obscures the glandular elements of these parts and the muscularis mucosa is indistinct, but the mucous membrane shows nowhere any fibrous or even maturing fibroplastic tissue. However, the sub-mucous coat presents marked thickening by well developed fibrous tissue. Within this occurs narrow or broad streaks and aggregates of small lymphoid cells following the course of lymphatics and perivascular spaces. These show here also marked dilatation. In the deeper portions of the sub-mucous coat the connective tissue assumes a hyaline, diffuse appearance. The underlying inner circular muscular coat is much changed. It shows marked hypertrophy. Within this musculature occur streaks and sometimes irregular, quite large, areas of cell infiltration, taking their origin apparently from lymph and tissue spaces. These

assume gradually sufficient dimensions to replace patches of musculature. The most recent smaller streaks and areas are made up of cells which are mostly of lymphoid character. In the older ones appear large and pale round cells with pale fibroplasts and a rather loose, thin, poorly nourished fibrillar tissue has developed which retains a number of pale, large, undeveloped, sometimes even necrotic, cells. This granulation tissue contains at no time new capillaries, and its nutrition is generally poor. Thus the muscular coat is interrupted and intersected throughout by these patchy, granulomatous cell infiltrations with loose scar tissue. A somewhat similar, but less extensive, state of affairs exists in the outer longitudinal muscular coat, and the adjoining serosa seems to be involved in places, but only little and very interruptedly.

" The enlarged glands which accompanied the specimen showed only inflammatory hyperplasia and lymph stasis."

Dr. Oertel then gives the following summary:

"Neither case is a cancer or a tumour. Both cases represent apparently closely related inflammatory changes within the stomach wall. These appear in the first case of more recent and active character than in the second. Throughout they carry the distinguishing feature of a granulomatous inflammation, which, in the second, has proceeded to much greater cicatrization. In both the sub-mucous coat suffers more severely and generally, while the first shows a characteristic endarterial involvement of the bloodvessels. In both cases occurs engorgement of bloodvessels and evidence of lymph stasis; in both the muscular coat is hypertrophied, and this is much more pronounced in the second and older case than in the first. This latter also shows an extension of the granulomatous process to the circular layer of the musculature. Finally, in both the serosa showed only slight and irregular involvement.

With regard to the genesis of the lesion:

In both cases, particularly in the first and more recent one, the impression prevails that the involvement of the glandular part of the mucous membrane is a secondary occurrence.

On the other hand, the lesion becomes manifest earliest in the sub-mucous coat and the lymphoid element of the mucous membrane, and extends through and around lymphatics and perivascular spaces to play most actively in the sub-mucosa. The localized superficial necrosis of glandular parts of the mucous membrane, therefore, is in all probability not an essential element of the lesion.

The hypertrophy of the musculature seems also to follow and to depend upon the changes in the sub-mucous coat, a view strengthened by the fact that the more recent first case showed much less of it than the second more advanced one. Furthermore, the granulomatous involvement of the muscular coat which occurred in the second and advanced case also impresses me as following the changes in the sub-mucosa.

From the foregoing it would appear that the cause of this peculiar granulomatous gastritis must be sought in an infection which reaches the stomach through, and progresses within, lymphatic channels. It is difficult to determine whether the infective agent gains entrance through the lymphoid elements of the mucous membrane or invades in the opposite direction from the outside. If one examines carefully the anatomical and histological findings of these and other cases from the literature, it seems that both channels of infection are possible. It is interesting to recall in this connection that in one of our cases a liver cirrhosis was demonstrable at the operation. The evidence in these and other cases indicates that, after the infection has once reached the stomach, and the lesion made its appearance, it may remain localized to the pyloric region or may spread and involve more or less the whole of the stomach.

How much lymph and blood stasis are contributory is open to question. These cases cannot be explained on this basis alone. With regard to the etiology: it is, of course, not possible to make any definite statement from these findings, particularly as our knowledge regarding other anatomical conditions in the body is very incomplete. That the features were those of a granulomatous inflammation has already been recorded, as well as the marked vascular changes in the sub-

mucosa of Case No. 1, but whether these cases were of a specific character, i.e., either tuberculous or luetic, must remain uncertain. The evidence was not sufficiently characteristic to establish this with certainty in either case and the lack of knowledge of other possibly contributory evidence in this regard, from other parts of the body, was lacking.

The objection that the lesion does not represent a gastritis in the strict sense of the term can hardly be regarded as valid, inasmuch as sooner or later practically all the coats of the stomach, including the glandular elements of the mucous membrane, may in certain cases even be the port of entrance.

It seems then that the term, Gastritis Granulomatosa Fibroplastica, expresses best the general anatomical character of the lesion."

Symptoms: The symptoms in most cases have not been particularly distinctive. It is more common in men than in women, although three of my five cases were females. In the early stages the symptoms are often suggestive of ulcer, i.e., pain or distress coming on ten or fifteen minutes after food. At a later stage vomiting occurs, and is generally followed by relief of the pain. The progress of the case is generally slow.

One would expect the X-ray examinations of the stomach to be of help, but I cannot say that they were of much value in the five cases that I have dealt with. The radiographer's report was either negative or erroneous. Further experience may teach us to read the plates better. My last case may be taken to illustrate the difficulties of the radiographer. The X-ray diagnosis was carcinoma. On the day of operation the plates were presented to the visiting surgeons present, all hospital men and men accustomed to looking at X-ray plates, and the unanimous opinion, in which I concurred, was that the condition was carcinoma. There was a definite filling defect at pylorus and in the region of the antrum. The same definite irregularities, angles and curves were repeated in all the plates. At a late stage these filling defects, if associated with lessened stomach capacity, might suggest fibromatosis or scirrhus. The

X-ray examination may, therefore, be of little value in the differentiation between the gastric fibromatosis and changes due to malignant disease. Nor have I found anything distinctive in the analysis of stomach contents. Free Hcl has been present in all my cases. The total acidity has not been excessively low. Lactic acid may be present. A few red blood cells may be found by the microscope. Hæmatemesis is rare. In advanced cases the contracted, thick-walled stomach may be felt in the epigastrum like a sausage-shaped tumour. One writer compared it to a cucumber. Examination of the blood may show a moderate degree of anæmia. There is loss of weight and strength. The disease is progressive and tends to destroy life.

A pre-operative diagnosis has only been made two or three times, based chiefly upon the presence of a tumour associated with a small contracted stomach. Even at the operating table it is impossible to determine definitely whether the thick-walled stomach is of the scirrhous or benign type. In the latter lymph nodes may be enlarged.

Treatment: The treatment is surgical. Resection of that part of the stomach involved is indicated for two reasons. First: At the operating table the operator cannot be sure that the disease is not scirrhous carcinoma. Second: It seems a fair assumption that the condition is one that might under favourable circumstances excite the growth of malignant disease. Other methods have in exceptional cases been followed by prolonged relief from symptoms. In von Eiselsberg's case the numerous adhesions rendered impossible a resection of the diseased area or even a gastro-enterostomy. He did a simple jejunostomy and the patient was well five years afterwards. Sheldons case was alive and well three and a half years after a gastro-jejunostomy, and other operators have had similar experiences. Finney reported a case that recovered after a simple exploratory operation. Of course, it is quite legitimate to question the correctness of the diagnosis in all cases where no part of the diseased stomach was submitted to microscopic examination.

In each of my five cases I resected the pyloric end of the stomach, as much of the antrum and fundus as was at all altered, and a bit of the duodenum. The openings in the stomach and duodenum were then closed and a posterior gastro-jejunostomy performed. The recovery in every case was smooth and quite satisfactory. The improvement in gastric digestion and general health was very marked, and I am satisfied that removal of the part of the stomach involved is the ideal method of treating these cases. When conditions forbid a resection, a gastro-enterostomy should be performed, or as a last resource a jejunostomy.

AMBULATORY TREATMENT OF SURGICAL TUBERCULOSIS WITH SPECIAL REFERENCE TO TUBERCULIN

By F. E. McKenty

(From the surgical service of Professor George E. Armstrong)

It is by no means an easy matter to deal with patients suffering from surgical types of tuberculosis who present themselves at the surgical out-door department of a hospital. These patients are, in the majority of instances, in very poor financial and social circumstances and cannot afford the necessary rest, fresh air and food. Indeed, the early records of this hospital demonstrate that these notoriously chronic affections require special efforts to obtain satisfactory results. Since 1914 we have, therefore, devoted special attention to these patients; regular tuberculin classes have been formed, and during these not only tuberculin is administered, but other available means are carried into effect. The patient gains thereby the feeling that something definite is being done. It stimulates him to follow instructions more intelligently and prevents him from becoming discouraged, thus drifting to other clinics.

Tuberculin, as a therapeutic agent, is more valuable in so-called surgical tuberculosis than in any other form. In many cases the results are too striking to be denied, the lesions show improvement after a very few doses have been administered, and rapidly progress to a complete and final cure. However, harmful effects are even recognized by its strongest advocates; its administration requires, therefore, careful selection of cases, close observation of patients and appropriate regulation of dose. Because of these requirements it has even been argued that tuberculin has no place in the dispensary treatment of surgical tuberculosis, but should be confined to patients under

hospital or sanitorium supervision. The experiences of this hospital out-door department fully justify its use under conditions I shall presently describe.

Our patients as a rule come from the more congested parts of the city; those requiring daily dressings come to the out-door department for that purpose. They are treated with the others, but once a week.[1]

When patients present themselves at the out-door for the first time a general examination is made to determine the presence or absence of tuberculosis in other parts of the body. Particular attention is given to the condition of the nose, throat and mouth, as our records, although not very complete, reveal at least 40% of cases under 15 years of age having enlarged tonsils and adenoids. These are attended to at once, and we have observed a number of cervical adenitis cases improve after removal of tonsils and adenoids. Again, in cases where improvement was slow or at a standstill, it was subsequently accellerated. Instructions are given regarding the care of the teeth, the necessity of plenty of fresh air and good food, and parents are requested to see that their children avoid crowded places (moving picture shows). Patients are advised to sleep on balconies or with their windows open and, where possible, thermometric observations are recommended to be carried out by patients themselves. For internal medication we have found that children do best with either Syr. Ferri Iod. or Syr. Ferri Phos. Co., while with adults a mixture of iron and malt is prescribed; if they are constipated, saline in the morning or liquid paraffin is recommended. All patients attending this Saturday clinic receive tuberculin. Other means of treatment, employed as adjuncts, will be mentioned in discussing the disease as it affects the different regions of the body.

VARIETY OF TUBERCULIN—ADMINISTRATION—DOSAGE

There is much difference of opinion regarding the best kind of tuberculin for therapeutic purposes. Sprengler and

[1] Saturday has been chosen partly because it is with these patients a half holiday, and partly because they can remain at home if a reaction after treatment occurs.

Raw believe in the superior immunizing power of bovine tuberculin against human tuberculosis, especially the surgical form; others favour the use of the old tuberculin. In our early cases the old was used, but as it was given irregularly no definite conclusions could be drawn from these. Since we started the systematic treatment of tuberculosis the B. E. obtained in commerce has been the one generally employed, and in giving it we have tried to follow, as far as possible, the rules formulated by Trudeau, i.e.:

1. Begin treatment with minute doses.
2. Raise the degree of tolerance to the highest attainable point by long continued progression of dosage.
3. Avoid local or general reaction as much as possible.
4. Follow no arbitrary rules as to the rate of increase or the maximum dose to be reached, but be guided merely by the degree of toxin tolerance in the individual.

Our initial dose for children was $1/30000$ mg. which has been gradually increased to $1/5000$ mg.; with adults the initial dose of $1/20000$, which in several of our cases we have, before treatment was completed, increased to $1/2500$.

Reactions: Reactions to tuberculin may be of three kinds: local, focal and general. The local reaction occurs at the site of inoculation (in our cases the left arm was used). The focal reaction occurs in the tuberculous focus itself. The symptoms of the former appear in from 12–24 hrs. after injection and last a few days. The symptoms of the reaction at the site of the tuberculous process depend upon the character of the lesion. The most important evidence of a general reaction is a sudden rise in temperature, which as a rule appears in about 12–24 hrs., may last several days, and associated with it there is commonly headache, chilly sensations, malaise and occasionally nausea and vomiting. When the patient returns the next week after the injection, careful enquiry is made for any of the signs or symptoms of these three reactions; if there is any evidence of intolerance, however slight, the next dose of tuberculin is omitted and the following week we begin with a much smaller dose. The few reactions noticed in this clinic

were mild, with the exception of two cases, both of which were followed by disastrous results (see under gland). In our selection of patients for this treatment those in which an active pulmonary lesion was present have been avoided.

The cases may be conveniently divided according to structures involved, i.e.:

1. GLAND. 2. BONE-JOINT. 3. GENITO-URINARY. 4. SKIN.

1. *Gland:* 65 cases of lymphatic gland involvement have attended this clinic in the past two and a half years. 15 left the city or otherwise disappeared from the clinic. 17 cases were double cervical adenitis, 15 left sided, 19 right sided, 14 sides not mentioned. 35 males, 30 females; the youngest patient was $3\frac{1}{2}$ years, the oldest 37. Glands in the parotid region were involved in 3 cases, suprasternal in 2 and axillary in 3. 1 case had tuberculous keratitis. 13 had discharging sinuses, 3 cases had very extensive skin involvement, extending from the sinus, involving in one case the neck and upper part of the chest. 2 cases had a moderately active pulmonary lesion (see later). The duration of treatment extended over a period of from three months in the shortest case to two years in the longest.

Whether we used tuberculin alone for treatment depended upon the presence or absence of caseation in the involved glands. The early cases, where there was purely a hyperplastic condition of the gland or, at all events, very little evidence of caseation, tuberculin was sufficient; on the other hand, if the glands were very much enlarged and showed evidence of caseation it was the custom to send the patient to the ward where the glands were removed and then tuberculin started. If an abscess had formed, this was evacuated, preferably by an open incision filling with Iodoform emulsion, 10%, and closing up tightly. This later treatment had at times to be repeated. Cases with discharging sinuses were injected with Bismuth paste 10% or Iodoform emulsion in addition to the tuberculin. In extensive skin involvement

around the openings of the sinuses, exposure to sunlight is recommended, but our main reliance is placed on the systematic use of X-ray. In this connection our results have been almost startling; one case, in particular, where the neck and chest were involved, cleared up, as far as the skin condition was concerned, in a few weeks.

Results of Treatment: Of the 50 patients under observation for $2\frac{1}{2}$ years, 32 are cured and have remained well; 8 had recurrence within 6 months after the completion of treatment; 8 cases of this original 50 are improved, but still under treatment. The two cases, referred to in the earlier part of this paper as having an unsatisfactory termination, were two brothers, æt. 9–11 respectively, with double cervical adenitis and an apical lesion that was fairly active. In spite of their pulmonary disease it was decided to try tuberculin. For a time they seemed to improve, but unfortunately, after 1/10000 mg. was given, they had a marked reaction (focal and general), after which, in spite of sanatorium treatment, they went rapidly down hill. These are the only two cases of this series in which tuberculin could be considered responsible for untoward results. Since that time we have advised against the dispensary use of tuberculin whenever active pulmonary lesions are present.

Changes in glands under treatment: Clinically the first change to be noted under tuberculin treatment is the gradual subsidence of periglandular infiltration. A mass in the neck which at first appears as a diffuse swelling with indefinite outlines, gradually diminishes in size, becomes sharply outlined; the individual enlarged nodes become distinct. These nodules gradually diminish in size until they disappear or become hard, pea-sized nodules. On the other hand, if caseation is at all marked (and especially is this apt to be so in children), a rapid breaking down process often occurs; while in adults calcification with fibrosis extending even into the surrounding tissue is a very common termination.

Histologically: The smaller nodules in the first or hyperplastic stage return to normal appearance, the only evidence of

previous disease being a thickened capsule. Those having been more severely affected, show replacement of gland by fibrous tissue; if caseation has occurred, these areas usually become calcified, while the remaining portion of the gland undergoes replacement by fibrous connective tissue which invades the periglandular structures. Thus the focus is walled off.

2. *Bones and Joints Tuberculosis:* In disease of these structures tuberculin has been used merely as an adjunct to other recognized forms of treatment: Bier's method has been used in a few cases when the disease affected the extremities.

Sinuses were injected with Bismuth paste, whenever it was considered necessary, and tuberculin given in the described way. In this manner there have been dealt with 4 cases of tuberculous dactylitis, 2 elbows, 2 sacro iliac joints, 1 knee, and 1 hip. Of these, the 2 elbow cases and 3 of the 4 cases of dactylitis are pronounced cured; while the remaining case of dactylitis, together with the hip, knee and sacro iliac cases, have shown improvement, but are still under treatment.

Bone tuberculosis seems to be very resistant to tuberculin treatment, probably because of the dead bone; until this is removed progress is bound to be slow.

3. *Genito-urinary Tuberculosis:* Tuberculosis affecting the genito-urinary apparatus is to be placed, as regards tuberculin treatment, in the same category as the previously mentioned bone and joint form, i.e., tuberculin is a valuable supplementary measure and indeed of great aid in combatting the disease. 10 patients have received treatment, 5 of which were cases sent to us with discharging sinuses after nephrectomy; the sinuses were injected with Bismuth paste and tuberculin given; 2 cases of unilateral orchitis had the testicle removed followed by tuberculin, given as a precautionary measure; 2 cases with double tuberculous orchitis were given tuberculin without any operative interference. These last 2 cases did not improve, sinuses soon formed and evidence of bladder and kidney lesions soon developed. The 5 nephrectomy cases mentioned above and the 2 unilateral

cases of orchitis did remarkably well. There was a rapid improvement in the general condition, shown by gain in weight and improvement in appetite. The sinuses completely closed, have remained so, and as far as can be ascertained there is no further progress of the disease in these cases where the testicle was removed.

4. *Skin Tuberculosis:* The combination of tuberculin with X-ray treatment in skin lesions has, in our experience, been followed by remarkedly good results. Naturally few cases were observed in the surgical out-door, as the majority go to the skin clinics. But we have treated some 9 cases in addition to those previously mentioned in that portion of the paper on the gland tuberculosis where the skin infection spreads from openings of old sinuses. These lesions were distributed as follows: 6 on leg, 1 on hand, 1 on nose and 1 very extensive lesion, involving side of neck, spreading up over cheek, reaching up to just below the margin of lower eyelid. This condition had been present for over ten years, and had resisted all other forms of treatment. After the nature of the disease had been determined by microscopic sections, the patient was put on tuberculin associated with X-ray treatment. It is scarcely two months since this treatment was started. To-day all that remains of this most chronic affection is a small area on the lower eye-lid.

Conclusions

1. Dispensary patients can be treated with tuberculin with safety and benefit.

2. Tuberculin has its greatest therapeutic value in gland cases.

3. The omission of the use of tuberculin in surgical tuberculosis, when no contra indications exist, seems to us an injustice to the patients.

4. The presence of an active pulmonary lesion is, in our opinion, a contra indication to its use as a dispensary measure.

AN UNUSUALLY LARGE EXTERNAL MYOMA OF THE STOMACH

By W. W. Chipman and C. T. Crowdy

(From the gynæcological service and the pathological laboratories)

Mrs. M. N., a iv para, aged 45, was admitted to the Royal Victoria Hospital on August 7, 1916, complaining of " a lump in the abdomen." This "lump" was first noticed about four years ago, when, in the patient's words, it was the size of a tea-cup. It gave rise to no discomfort.

In February of this year, however, the patient began to complain of a dragging, tired feeling in the abdomen, was troubled with attacks of vomiting, and noticed a decided increase in the size of the tumour. The menstrual habit was in no way disturbed. These symptoms and signs became more marked, and the patient was finally admitted to hospital in August.

The physical examination of the abdomen showed a tumour mass, the size of a cocoa-nut, in the region of the hypogastrium. It was apparently pelvic in origin, and extended upward to within two fingers' breadth of the umbilicus. It was globular, movable, firm in consistence, somewhat nodular, and distinctly insensitive. On percussion no bowel lay in front of it, and it lay within the peritoneal cavity. The spleen and both kidneys were in their usual position.

A pelvic examination discovered the lower pole of this tumour occupying the pelvic inlet, and the body of the uterus could not be disassociated from it. The ovaries were distinguishable, and the rectum and bladder were not displaced.

A diagnosis of fibro-myoma uteri was made, and the patient submitted to operation on August 11th.

The abdomen was opened in the mid-line, and the tumour was found completely surrounded by omentum, and in no way attached to the pelvic viscera. It was greyish-yellow in

colour, firm, nodular, intra-peritoneal, and was evidently
nourished in part by the omental vessels. Only after the
tumour was enucleated from its omental bed was it discovered
to be growing from the posterior wall of the stomach, near the
greater curvature.   Its attachment to the stomach measured
five centimeters in length and two in breadth, and was an
extremely vascular pedicle.   In dividing this pedicle I (Chip-
man) entered the stomach cavity, and accordingly I was com-
pelled to resect a portion of the stomach wall.   As at this time
the tumour was considered malignant I incised a peri-pedicular
zone of stomach wall, some three centimeters in breadth, and
removed it with the tumour.   The stomach mucosa was found
everywhere healthy.   I closed the stomach in the usual way
with through and through sutures, and a superimposed layer
of Lembert sutures.

A further examination showed a healthy stomach, with
no marked degree of ptosis.   In the lesser omentum were
several enlarged lymph glands.   One of these, the size of a
filbert, I removed.   There were no nodules in the liver; the
gall-bladder, duodenum, and pancreas were healthy.

The patient's recovery was complicated by a phlebitis in
the right leg. This, however, soon subsided, and she left hospi-
tal, completely relieved of her symptoms, on September 13th.

From the first her vomiting ceased, and the digestion
quickly improved.

On section the tumour was found to have undergone a
central hæmorrhagic necrosis. This central cavity, with
ragged necrotic walls, contained about 250 c.c. of blood-
stained fluid.   When this fluid was removed, the tumour
weighed 1475 grm. It was almost circular in outline, save
for a small knob or boss, situated near the area of its stomach
attachment.   This area of attachment measured 5 by 7 centi-
meters, and can be plainly seen in Plate I.

In Plate II the tumour will be seen to resemble very closely
a myoma of the uterus.   It was enclosed by a thick fibrous
capsule, and was largely composed of interlacing bundles of
smooth muscle tissue. A marked feature was an advanced

cystic degeneration, which took the form of irregular cavities lined by necrosed tissue, and filled with a thin blood-stained fluid.

Microscopic sections taken from the growth (Plate III) proved it to be a leio-myoma, which had grown directly from the smooth muscle of the stomach wall as a pedunculated tumour. No other tissue was found, and the several sections differed only as they showed more or less degenerative change.

A section of the stomach wall showed a well-preserved mucosa (Plate IV), no hyperplasia of glandular epithelium, and a well-defined basement membrane.

The lymph-gland disclosed only inflammatory change, evidently reactionary to the absorption from the tumour.

Myomata of the stomach can be divided into two groups:

1. Internal, intramural or submucous, which project into the lumen of the stomach. These are the most frequent type of this tumour. They are mostly small, occasionally multiple, and rarely assume a larger size, when they may give rise to severe hæmorrhage from the stomach. Such a case was, for instance, reported to the Association of American Physicians some years ago by the elder Janeway.

2. The second form is represented by external, usually pedunculated, tumours which are much rarer, but may assume a tremendous size. This type of tumour is particularly misleading diagnostically, for it is able to execute free and wide excursions, and may, therefore, locate in different parts of the abdomen or, as in this case, in the pelvis. The number of these tumours, so far reported, is small. Kaufmann (Pathologische Anatomie 1911, vol. I, p. 443) mentions one case in a woman of 56 years, in which a tumour of 2,325 grm., being attached by broad base to the small curvature, had descended to the brim of the pelvis and simulated an ovarian tumour. Tortion of the axis caused symptoms of incarceration.

In what is probably the most extensive study of myomata of the gastro-intestinal tract by Steiner (Beitrage zur Klin. Chirurgie von Bruns., xxii, p. 1, 1898), we find only three cases of external myomata which had reached considerable size.

The first is one reported by Eppinger in a 60 year old man, in which the tumour had reached the size of 14 cm. length and 26 cm. breadth, its weight not given; it took its origin from the larger curvature of the stomach, that is, its longitudinal muscle system. It projected into the lumen of the stomach only to a very slight extent; the largest part of it was outside. The second case is one by Erlach, in a woman of 33 years, in whom a mass occurred in the left abdominal quadrant. This movable, globular tumour, which on operation showed connection with the smaller curvature of the stomach, had by its weight, drawn the stomach into form of a tube which resembled the large gut. This tumour had a weight of 5,400 grm., and was as large as a man's head.

The third is a case of von Eiselsberg, in a woman of 30 years, who complained of increase in abdominal size and a hard tumour in the abdomen. The lower part of the abdomen disclosed, on examination, a large projecting globular tumour, intraperitoneally, and extending to the symphysis; it possessed a smooth base and its surface was firm. It was movable, and attached to it appeared another nodular tumour, size of a man's fist. Clinical diagnosis was ovarian tumour. Operation disclosed attachment of the tumour to the greater curvature of the stomach by a peduncle. Section of the peduncle, and removal of the tumour. The tumour weighed 5,500 grm. and consisted of a number of large nodules; the main parts of the growth were firm and œdematous, only in the centre was a well circumscribed, smaller, grayish, soft node.

Microscopic examination showed fibro-myomatous character of the growth throughout. In the softer, central nodule, fibro-sarcomatous tissue was found. The musculature of the stomach was generally lost. The origin of the growth in this case seemed to be the submucous connective tissue.

Besides these large tumours, Steiner has collected and described a number of smaller ones, as well as a few malignant sarcomatous myomata and fibro-myomata which have no direct concern in our case.

Further search has not disclosed to us reports of similar large pedunculated gastric growths which can be included in our class, although descriptions of a number of smaller tumours are scattered through the literature. (See: Mourigound et Gardere, Le Leiomyome Pedicule externe de l'Estomac. Archives de Médecine experimentale, Charcot, 1910. *Also:* John L. Yates, M.D., Sarcoma and Myoma of Stomach, Annals of Surgery, Vol. xliv, 1906.)

As far as the histology and histogenesis of these tumours are concerned, our investigations indicate that the origin must be found in the smooth muscle of the stomach wall. The mucous membrane itself, as well as the submucous tissue immediately above the growth, were apparently intact; therefore, we fully agree with the conclusions of Steiner, who upholds the original conception of Virchow in the muscular origin of these tumours.

These tumours of the stomach have rarely, if ever, been diagnosed; only after the abdomen has been opened have they been identified. In the present case, to all physical examination, the tumour fulfilled the conditions of a pediculated fibromyoma of the uterus. The history of the patient was also of little assistance, for through the stomach distress and vomiting were conspicuous features, these symptoms and signs are frequently encountered in the true pelvic neoplasm.
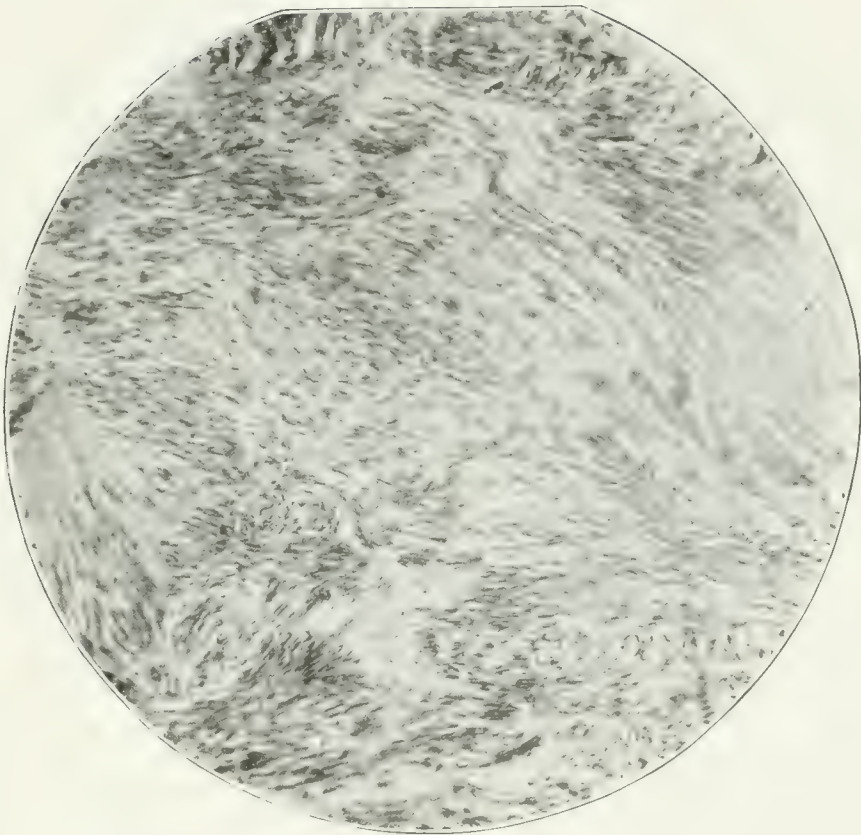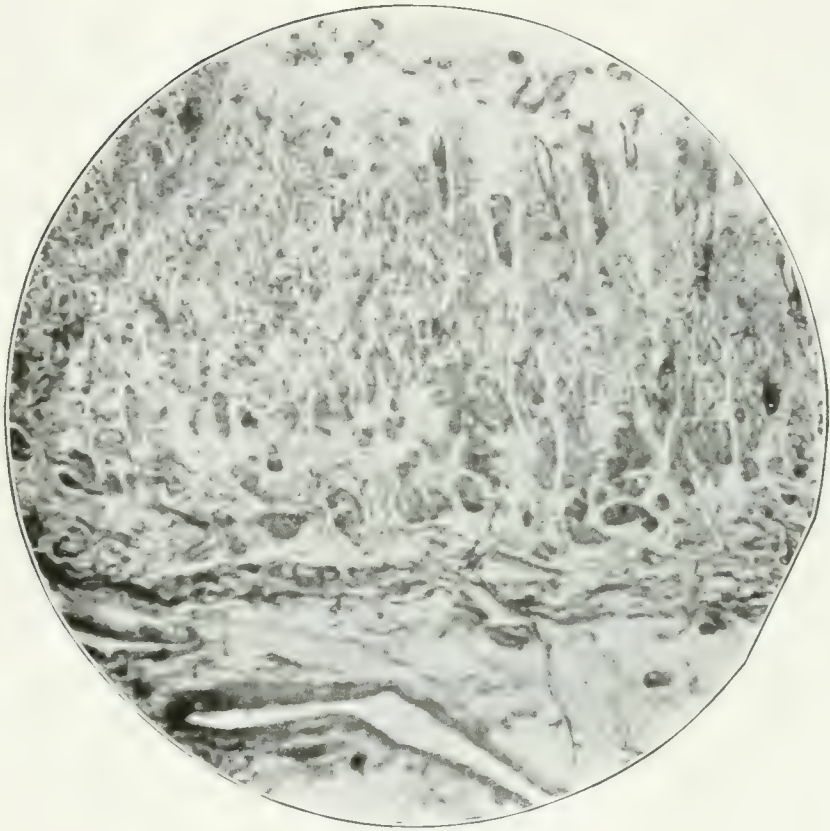
Fig. 1

FIG. 2

Fig. 3

Fig. 4

PYOSALPINX COMPLICATING ECTOPIC GESTATION*

By John R. Fraser

(From the gynæcological service of Professor W. W. Chipman)

The association of pyosalpinx with ectopic gestation is of sufficient rarity to prompt the report of the following case.

Mrs. E., æt. 28, was admitted to the Royal Victoria Hospital, Montreal, in the service of Dr. Chipman, on September 5, 1915, with the following complaints: Pain and tenderness in the hypogastrium, slight bloody vaginal discharge.

The history dates back to May 15, 1915, when she had the last period; she was well till August 20th when she was suddenly seized with severe colicky pain in the lower abdomen and brisk vaginal hæmorrhage. With rest in bed the symptoms subsided in a few days, with the exception of slight vaginal hæmorrhage. On September 4th, after being up and working about the house, she was again seized with severe colicky pain in the lower abdomen, especially on the right side. From this time on the symptoms became progressively worse—the pain increased in severity. There was vomiting and fever.

In her previous history she notes that she had two normal pregnancies, the last five years ago, and in the past three years two abortions. There has been no other illness.

On admission she was found to be acutely ill with temperature 102°, pulse 132, respirations 36, and she presented all the evidences of an acute infection. The heart and lungs were normal. The abdomen was moderately distended, the lower half being fixed; the respiratory movements were confined entirely to the upper abdomen.

The flanks were not bulging, there was tenderness and muscle spasm over the lower quadrants the uterus was palpable lying in the mid-line slightly above the pubis. It was not possible to make out the appendages because of the tenderness. Per vaginam, there was some evidence of a previous gonorrhœal infection, as shown in the swelling of the Bartholinian orifices and granulation of the vaginal mucosa. The urethra and Skenes follicles were free. A little bloody vaginal discharge lay in the lower vagina. The cervix was normally placed, firm and closed; the uterus was small, anteverted, and anteflexed, and fixed. The post formix was bulging and very tender. Through the lateral fornices it was possible to make out masses on each side, on the right the mass was more or less diffuse and easily the size of a grape fruit. On the left it was more clearly defined and the size of a small orange. The urine was normal.

As her condition did not warrant immediate intervention she was treated with stimulation and kept supported in Fowler's position. The following morning there was improvement in the general condition; pulse and temperature were lower. Toward evening abdominal pain and distress aggravated her condition considerably. Locally there was mere bulging of the fornices, notably the posterior, and it was thought to be possible to map out masses, on either side of the abdomen low down.

On the morning of the third day all of these signs were more marked and operation was deemed advisable. The ordinary posterior colopotomy was done first and the presence of blood in the posterior cul-de-sac verified. A laparotomy was then performed. Clear fluid escaped in considerable quantity, the pelvis was found filled with a large inflammatory mass, covered over with omentum; when this omentum was lifted off and the true nature of things revealed a large tuboovarian abscess was found on the right and a ruptured tubal pregnancy on the left.

The right tube, ovary and abscess sac were removed first, then the left tube with gestation sac. The left ovary was

left behind. The pregnancy had occurred in the ampullary portion, and rupture, had occurred at this point into the free peritoneal cavity. A fœtus approximating seven weeks development was found in the centre of the blood clot at the point of rupture, the uterus was removed and vaginal drainage established. Before closing the abdomen three ounces of ether were injected. The course post operative was uneventful and she left the hospital in good condition.

The case may be said to be interesting from these standpoints: the obscurity of diagnosis, its relative rarity and its etiological bearing.

The symptoms on admission, pain in the lower abdomen of severe character, temperature of 102° with a considerable degree of peritonitis associated with the findings on examination of bilateral appendage masses with a correctly placed uterus, together with the undoubted evidence of Neisser infection, all prompted the justifiable diagnosis of bilateral salpingo-oophoritis, with an exacerbation.

Accordingly, the treatment of rest in bed, in the Fowler position, ice bag to abdomen, and stimulation, was in just accord, with the well recognized treatment of salp. oophoritis, "watch and wait" for the so-called "cold stage."

However, the rapid increase in the size of masses, the increased bulging of the fornices, the so-called crepitations (that is the peculiar sensation imparted to the examining finger by blood clot) with increasing degree of shock together with the history of amenorrhœa, all prompted one to the diagnosis of a possible ruptured extra-uterine pregnancy and led to the exploratory posterior colpotomy.

In a brief survey of the literature one is impressed with the rarity of the condition. Coues of Boston, in 1911, reported a series of 214 cases of ectopic gestation with a review of the literature, in which he found that roughly 16% of the cases only showed evidence of disease in the opposite tube, and none showed such an advanced condition as this, the majority exhibiting a mild catarrhal salpingitis or a few adhesions about the fimbriated end.

The writings of Kaufmann, Aschoff and Billroth, are in accord with the above; i.e., in the large majority of cases the presence of catarrhal changes in the tubes at most would represent the condition found.

Perhaps the chief interest centres in the light which this case throws on the etiology of ectopic gestation. At the 1911 meeting of the American Gynæcological Association, in the discussion of Dr. Smith's paper on "Recurrent Ectopic Gestation," the matter of etiology was dwelt upon by Drs. Chipman, Pollack and Fry. Dr. Chipman stated that the prevailing opinion of the time in regard to this matter was to recognize two great classes or causes:

1. Those due to congenital causes.
2. Those due to inflammatory causes.

In the first great group one notices a fœtal type of tube with imperfect growth, a tube which has a thin wall, poor musculature, thin mucosa, with an absence of, or a weak, ciliary action, and ofttimes persistence of the fœtal convolutions.

In the second or inflammatory type a previous inflammation, usually of mild degree, has caused destruction of surface epithelium, with consequent loss of ciliary action; also there may be fusion of the mucosal folds or obliteration of the proximal end of the tube.

This case very well shows the effect of inflammatory processes on the tube and bears out the above statement. It is interesting to note that even with what appears to have been a sharp infection pregnancy should have occurred at all.

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THE TREATMENT OF GLAUCOMA BY ELLIOTT'S OPERATION

By John W. Stirling

(From the ophthalmological service)

The successful treatment of simple glaucoma has been and is one of the most urgent problems in the therapeutics of the eye.

It has taxed the ingenuity and resources of ophthalmic surgeons for years, and the results until lately have been far from satisfactory.

The exhibition of eserin for a prolonged period and the classical iridectomy of von Græfe have been the principal methods, having for their aim the opening up of the angle of the anterior chamber and allowing of freer escape of the intra-ocular fluids.

Many modifications of the operative procedure have been essayed with more or less, and generally less, success.

Within the past few years Col. R. H. Elliott has brought forward his method of trephining, with the resulting permanent subconjunctival fistula, which promises more than any other method yet tried.

The period of probation for this operation may be considered as almost past and its value accepted as based on a firm foundation.

Nevertheless, there are objections urged against the operation and much discussion over it, so that the publication of results obtained by this method are of value.

I accordingly present a series of cases—consecutive, not picked, from my own experience.

The main point brought against the Elliott operation is the possibility of the late infection of the eyeball with its almost certain loss.

With any operation there is risk, but it is held, and rightly, that the existence of the permanent fistula, protected only by a thin conjunctival covering, is a standing menace.

The conjunctiva can be ruptured by a slight trauma and a path left open for infection; more especially is this possible in elderly patients, who are the most frequent victims of this disease and in whom the conjunctiva has a tendency to become friable if the glaucoma be of long standing.

Avoidance of button-holing the flap, and at the same time endeavouring to dissect off as much of the episcleral tissue as possible with the flap in the region of the proposed trephine hole, help to minimize this danger.

Fortunately in the clinic at the Royal Victoria Hospital we have as yet out of a total of eighty-four operations not one of these direful results to report.

Another source of trouble in this operation is the occasional blocking of the trephine opening at a varying period after the operation. The blockage can be due to uveal tissue forced into the opening, this generally arising from the trephine opening being too far back from the corneal edge. This is avoided by splitting the cornea at the limbus and making the trephine opening well forward, at least half the diameter of it being in the apparent corneal tissue. This complication has not troubled me, but another type of blockage has been the cause of failure in three operations out of forty-six.

This latter form of blockage is due to a hyperplasia of connective tissue from the adjacent episcleral and scleral and probably uveal tissues, which gradually closes the trephine opening and binds the superjacent conjunctival tissue down over it—there is no protrusion of uveal tissue.

Col. Elliott attributes it to some mild type of infection.

The cases I have observed it in have been of the chronic congestive type, and a carefully done trephining repeated at another point in the corneal limbus was followed by the same result in two of the cases.

The three cases I will give in further detail, as being instructive; all three were in elderly people, with well marked arterio-sclerosis and high blood pressure.

The first case (No. 21 in my table) had lost the left eye ten years previously from glaucoma, despite the performance of two iridectomies and a Priestly Smith scleral incision. There had been prodromata, so called, for some months before I saw the patient for the right eye. When I was called in, a subacute acute attack was on, which in a few hours became acute in its intensity. Remembering the failure of the iridectomy in the other eye, I performed an Elliott operation with peripheral iridectomy forthwith; relief was rapid, but after twenty-two days the symptoms returned, the opening was blocked and the conjunctiva bound down. I dissected off the conjunctiva and cleared the scleral opening, and the symptoms of pain disappeared, only to return with a further blocking in ten days. A second trephine opening was now made at another point of the corneal circumference with temporary relief, but the same phenomena recurred.

On return of the symptoms, as the patient objected to the removal of the eye, I trephined the sclera in the equatorial region, cauterizing the edge of the wound; despite this, the symptoms again recurred after a few days and, as a last effort, I removed a large triangular flap of the sclera at the equator with scissors, etc.; this was followed by permanent relief of pain, and vision of hand movements down and out, which vision, however, in the course of a year had disappeared. No. 15 was a congestive case which had been trephined elsewhere some months before; the opening was closed by fibrous tissue and tension was up. I trephined afresh, but in the course of three weeks symptoms recurred and the eye was enucleated—as yet I have no report of the pathological findings of the case.

The third case No. 11 was one of long standing glaucoma which had had an iridectomy performed some years before, but was nearly blind and suffering pain. The Elliott operation was followed by entire relief, but a year later the opening

had slowly closed, symptoms had returned and the eye had to be enucleated on account of pain.

Cases of severe hœmorrhage into the vitreous, entailing the loss of the eye, have been reported. It is easily conceivable that the sudden relief of high tension, with sclerosed vessels, would result in vascular rupture. How it does not occur more frequently is a surprise, when one observes the force with which the aqueous is ejected in some cases.

In three cases of mine there was rather free hœmorrhage into the anterior chamber from vessels at the base of the iris, but this readily cleared up. In none was there severe hæmorrhage into the vitreous following the operation.

Loss of vitreous, I have to report in one case. The eye had been the seat of chronic glaucoma for many years, was blind, the iris atrophied and attacks of sharp pain developed; tension was high. On finishing the trephining, there was a squirt of aqueous followed by a little blood and fluid vitreous, the latter evidently due to a slight rupture of the degenerated suspensory ligament. Recovery was uneventful and the tension has remained subnormal.

These accidents, with other risks, are to be looked for in elderly patients with history of prolonged glaucoma, and cannot be urged against the Elliott operation, as they have to be faced in iridectomies and other operations.

Slow formation of the anterior chamber is not rare, and as a rule is of slight import, being generally due to free drainage into the subconjunctival space. The longest period I noted in my own cases was fourteen days, and the final result of the operation was good.

Cataract occurred in three cases coming on nine months or more after the operation. These cases were characterized by a fairly high tension, and after the operation a persistent low one of ten to fifteen degrees (by the Schiotz Tonometer), the diminished intraocular pressure interfering with the nutrition of the capsule and secondarily of the lens.

By referring to my table it will be seen that I report thirty-six cases and forty-five operations.

Eight operations were done for acute and subacute conditions; of these, two were failures, being in case No. 21 reported above.

Twenty-seven operations were done for chronic glaucoma. One case, No. 10, was operated on by Col. Elliott during his visit here. In these there were two failures, one being Case No. 15 and the other, No. 11, reported fully already.

Six operations were for secondary glaucoma. In two there was an old dislocation of the lens into the anterior chamber, the trephining resulting in lowered tension and abolition of pain. In another case there had been kerato-irido-cyclitis of long standing following an explosion, and here the tension was 30° after the operation. Four other cases followed iridocyclitis with ring synechia; here the result in one case was very marked (No. 29) the tension falling to 20°, together with the disappearance of the pain, in another tension fell from 90° to 30° and in a third from 50° to 18°.

The last one (No. 30) was unruly and on the third day pulled the bandage off the eye, rubbed it and brought on a severe intra-ocular hæmorrhage, for which I had to enucleate the eye.

The results of the trephine operation in three cases of ulcer of the cornea were very brilliant.

The ulcers were of the large, rather superficial torpid type with increased tension.

One case of keratectasia in the weak scar of an old ulcer was followed by diminution of fully a half of the ectasia, which diminution had persisted for several months when last seen.

Thus, out of the forty-five operations four failed; one was lost from traumatic late hæmorrhage; the remainder were successful, in varying degree, in diminishing tension, relieving pain and improving vision.

As regards the Elliott operation, in nearly all cases I did a peripheral iridectomy; it does not complicate the operation and, I feel, is safer. Moreover, in most cases, especially if there is any marked tension, the iris bulges into the opening and the prolapse has to be excised. The button-hole thus left is not disfiguring and enhances the drainage.

In about thirty per cent. of my cases there were mild symptoms of iritis, which, however, rapidly disappeared without untoward result, if one excludes the possible presence of it in the cases of blocking above referred to. The instillation of atropin the day after the operation was a regular procedure.

The special field for this operation has so far been chronic glaucoma, and the earlier the operation is done the better.

In chronic glaucoma of long standing so many degenerative changes can occur—the friable iris, degenerated suspensory, ligament, vascular changes, etc., that complications may be looked for in operating.

I find the Priestly Smith Scotometer of great use in the very early stages, discovering the Bjerrum symptom when other signs may be very indefinite.

However, a discussion of the diagnosis and symptoms of glaucoma would lead me outside the subject matter of this paper.

The Elliott operation certainly secures good drainage, which is our one main object, and just so surely as we get this we must run the risk of a chance of late infection. Therefore it remains to be seen if any improvement can be made by which this risk is minimized.

The method of operating calls for no special note, the aim in the first step being to elevate as much subconjunctival tissue as possible, more especially in the area of the trephine opening; next the splitting of the cornea so as to get the opening well into the anterior chamber, the use preferably of 1.5 trephine. In replacing the conjunctiva rarely is a stitch necessary.

No.	Date	Name	Age	V. Before	T. Before	Field Before	V. After	T. After	Field After	Diagnosis	Opr. and Notes
1	Sept. 10/12	E. G.	65	Sept. 21/13 L.E. fingers at 4 ft.	L. 35	Small area 10° temporal side of fixation point	1/60	20	Increased 10° further to temporal side	Chronic Simple Glaucoma	Elliott iridectomy
				Nov. 20/12 R. E. 2/60	60	30° to temporal side remains	3/20	25	Field slightly increased	Chronic Simple Glaucoma	Elliott iridectomy
2	Nov. 9/13	Mrs. L.	56	Oct. 31 L. E. fingers 5 ft.	55	Nasal half gone, temporal contracted to 35°	6/12	25	Increased 10° to temporal side	Chronic Simple Glaucoma	Elliott iridectomy
				Dec. 15/12 R. E. 6/60	52	Same, but temporal limit 50°	6/60	20	Temporal limit unchanged, but nasal limit it now 25°	Chronic Simple Glaucoma	Elliott iridectomy
3	Nov. 9/13	Mrs. McI.	57	L. E. 6/24	50	Nasal side gone, 35° to temporal side	6/12 with lenses	15	Field unchanged	Chronic Simple Glaucoma	Elliott iridectomy, cataract 9 months later
4	Jan. 3/13	A. R.	65	Hand movements at 6 inches to outside R. F. +2D.	85	Small upper outer quadrant remains	6/60 fell back later	26	Unchanged	Subacute Glaucoma and Chronic	Elliott iridectomy
				June 17/13 L. 6 60 +2D	67	Nasal half gone	6/60	35	Field increased 15° to temporal side	Chronic Simple Glaucoma	Elliott iridectomy
5	Mar. 16/13	Mr. O.	54	R. E. 6/12 +1.25D +0.75D ax. 70°	45	Nasal side contracted 20°	6/6	10	Nearly full, increased 10°	Chronic Simple Glaucoma	Elliott iridectomy, secondary cataract 1 year later
6	April 19/13	Mrs. McD.	68	L. E. 2/60 +4D	48	Nasal field gone	5/15	18	Unchanged	Chronic Simple Glaucoma	Elliott iridectomy 8 days before a.c. reformed R.E. lost from Chronic Glaucoma

No.	Date	Name	Age	V. Before	T. Before	Field Before	V. After	T. After	Field After	Diagnosis	Opr. and Notes
7	April 10/13	S. B.	50	6/6+0.5D	45	Marked contraction nasal field, espy. in upper quadrant	6/6	22	Field increased by an average of 10°	Chronic Simple Glaucoma	Chronic Glaucoma 5 years A.C. formed after 14 days Elliott iridectomy
8	June 9/13	Mrs. R.	60	6/6 R. E.	26-40	Upper nasal, extending to temporal quadrant, missing	6/6	15	Field increased by 10°	Chronic Simple Glaucoma	Elliott iridectomy. Highly nervous subject, curious variations in tension during the day.
				6/6 L. E.	40	Upper nasal, extending to temporal quadrant, missing	6/6	20	Field increased by 10°	Chronic Simple Glaucoma	Elliott iridectomy. Highly nervous subject, curious variations in tension during the day.
9	July 28/14	T. T.	68	L. E. fingers at 6 inches to temporal side	50		Hand movements 2 ft.	19		Chronic Simple Glaucoma	Elliott iridectomy. Subac. Glaucoma 1 year ago, relapsed Subac. attack diminishing into present chronic state
10	June 22/14	J.W.	64	R.6/60+7D=6/7	87	Superior nasal gone and part of superior temporal gone	6/6 with lenses	25	Marked increase of field, but upper nasal missing	Chronic Simple Glaucoma	Elliott iridectomy, by Col. Elliott
				L.6/60+7D=6/7	80	Field generally limited, but especially to inner side	6/6 with lenses	20	Increase by 10°	Chronic Simple Glaucoma with subacute exacerbation	Elliott iridectomy, by Col. Elliott

No.	Date	Name	Age	V. Before	T. Before	Field Before	V. After	T. After	Field After	Diagnosis	Opr. and Notes
11	Aug. 20/14	Miss C.	70	R. E. fingers 6 inches to temporal side	45	Inner half of field gone and temporal reduced by 30° to 40°	Unchanged	20	Field unchanged	Chronic Simple Glaucoma	Old iridectomy years ago, now tension up and pain. Elliott iridectomy. Tension rose again a year later and eye enucleated for pain—blockage of trephine opening by fibrous tissue
12	Jan. 7 14	Mrs. G.	60	H. E.—1D ax 90 6/12.50 L. E. lost from Simple Glaucoma	50	Lower and inner half gone	6 12	15	Increased by 10°	Chronic Simple Glaucoma	Elliott iridectomy
13	Dec. 12 12	G. P. G.	80	R. E. blind fr. Glaucoma L. E. 6 9 +0 5D ax 70	60	Limited to 15° to nasal 50° to temporal side	6 6	15	Slightly increased	Chronic Simple Glaucoma	Arterio Sclerosis-Diabetes. Elliott iridectomy. In 1 year cataract began to develop
14	Jan. 14 14	Mrs. A.	70	R. E. 6 10 L. E. No. p. l.	40 80	Reduced to 20° to nasal side No p. l.	6 6-0.75D ax 160	20 10	Increased 10° No p. l.	Chronic Glaucoma Chronic Glaucoma 9 years	Elliott iridectomy Elliott iridectomy for pain, slight haemorrhage into a.c., iris friable, came away in pieces, also some fluid vitreous escaped, eye finally very soft

No.	Date	Name	Age	B. Before	T. Before	Field Before	V. After	T. After	Field After	Diagnosis	Opr. and Notes
15	Mar. 4 15	S. R.	63	L. E. p. l. to outer side	100	P. l. to outer side only	P. l.	30		Chronic Congestive Glaucoma	Elliott operation 1 year ago; now pain again; Elliott & iridectomy; iris rotten; tension rose in a month, opening blocked by fibrous tissue had to enucleate—congestive type of glaucoma
16	May 1916	R. C.	50	1/10	85	Small area out from fixation point	1/10	25	Unchanged	Chronic Glaucoma	Elliott iridectomy
17	Mar. 13 15	N. T.	40	R. E. 6/6 −3D−1D ax 115	40	Only small portion of inner lower quadrant and one half outer lower quadrant left	6/6	10	Marked increase of field 15°, but upper portion missing	Subacute Glaucoma and Chronic	Elliott iridectomy, iris rotten and anterior peripherl. synechia cupping not quite to edge of disc
18	Oct. 21/14	Mrs. R.	64	R. E. 6/12 L. E. 6/12	60	Nearly all nasal half gone & temporal much reduced	6 6	25	Increased 15° on temporal but hardly at all on nasal	Chronic and Subacute Glaucoma	Elliott iridectomy, recurring haze, but no typical cupping
19		Mrs. M.	48	R. E.	90		No p. l.	10		Chronic Absolute Glaucoma	Elliott iridectomy for pain
				L. E. 5/10	35	General contraction more marked nasal side	5/7	18	Increased 10°	Chronic Glaucoma	Elliott iridectomy for pain

No.	Date	Name	Age	V. Before	T. Before	Field Before	V. After	T. After	Field After	Diagnosis	Opr. and Notes
20	Jan. 8/14	Mrs. K.	74	L. E. no p. l.	95	No p. l.	No p. l.	18	No p. l.	Chronic and Subacute Glaucoma	Opr. for pain; Elliott iridectomy
21	Dec. 14/13	Mrs. McP.	58	R. E. Tn. 52°; 85° by night	Tn. 52			18	28	Acute and Subacute Glaucoma	Elliott iridectomy
				Jan. 8, Opg. blocked	96				Jan. 21, globe soft		Reopened trephine hole Elliott on nasal side of cornea
				Jan. 18, Opg. blocked							
				Jan. 24, Opg. blocked	85				20		Equatorial scleral trephine and cautery
				Jan. 31, Opg. blocked	85				Hand movements at 3 ft. to outer side 25		Excision triangular flap, from sclera far back. Alb. and blood in urine, choroido-retinitic patches in macula region
22	June 10/15	Mrs. McL.	58	R. E. No p. l.	90		No p. l.	30		Subacute Glaucoma	Elliott iridectomy done for pain
23	Oct. 21/14	Miss B.	68	L. E. 6/24	45	Nasal half gone	6/6	15	15° increase in field	Subacute Glaucoma	Elliott, no iridectomy

No.	Date	Name	Age	V. Before	T. Before	Field Before	V. After	T. After	Field After	Diagnosis	Opr. and Notes
24	May, 1916	Mrs. V.	68	R. E. p. l.	90	Patient's statements too uncertain to judge field	5/30	18		Subacute Glaucoma	Just over acute attack in R.E. —now subacute—Elliott iridectomy
				L. E. 6/60	50		5/30	20		Chronic and Subacute Glaucoma	Elliott iridectomy
25	May 4 15	A.	51	R. E. fingers 1 ft.	65	Greatly limited, only small area to temporal of 15° remains	5/15	15	Unchanged	Subacute and Chronic Glaucoma	Elliott iridectomy
26	Sept. 21 15	L. B.	66	No. p. l.	50	No p. l.	No p. l.	20		Secondary Glaucoma Subacute	Elliott iridectomy for pain —successful
27	Oct. 28 13	W. L.	61	R. E. no p. l. L. E. no p. l.	90		No p. l.	30		Secondary Glaucoma to partially detached retina	Elliott iridectomy for pain —successful B. P. 210
28	Sept. 17 14	J. S.	24	R. E. blind.	75		No p. l.	35		Secondary Glaucoma	Dislocation of lens into anterior chamber — staphyloma, secondary glaucoma —pain, Elliott relieved pain and lowered tension

No.	Date	Name	Age	V. Before	T. Before	Field Before	V. After	T. After	Field After	Diagnosis	Opr. and Notes
29	Feb. 3/15	T. R.	46	R. E. no p. l.	80		No p. l.	25		Secondary Glaucoma to old Iridocyclitis and ring Synechia	Elliott iridectomy for pain — secondary glaucoma. Sharp reaction but in 15 days eye quiet and tension 25
30	April 2 13	A. M.	12	L. E. no p. l.	42					Secondary Glaucoma to old Iridocyclitis	Elliott iridectomy for pain and tension—patient unruly, restless —rubbing eye, pulled off bandage; haemorrhage 3 days later, had to enucleate eye for pain
31		L. C.		?Hand movements	70		Unchanged	30		Secondary Glaucoma following injury and Iridocyclitis	Elliott iridectomy
32	July 25/14	Miss McD.	23	3/20	50	General limitation most marked to nasal side	3 18	18		Secondary Glaucoma to Iridocyclitis	Elliott iridectomy

No.	Date	Name	Age	V. Before	T. Before	Field Before	V. After	T. After	Field After	Diagnosis	Opr. and Notes
33	Jan. 30/13	A. P.	18							Keratectasia	Elliott for ulcerative ectasia — marked diminution of cornea — persisting staphyloma 3 mos. later
34	Feb. 7/13	F. A.	45	L. E. 6/12	35		6/12	25		Large superficial ulcer; cornea failed to heal under paracentesis	Elliott operation; healed in 4 days
35	Feb. 7/13	A. W.	59	L. E. 6/60	45		6/60	18		Central ulcer cornea	Elliott—healed in 9 days
36	Jan. 16/14	Miss B.	69	No p. l.	48	No p. l.	No p. l.	25		Absolute Glaucoma—ulcer cornea	Elliott iridectomy for ulcer and pain — healed in 12 days

TUBERCULOUS MENINGITIS WITH SPECIAL REFERENCE TO THE TUBERCLE OF THE CHOROID AND ITS PATHOLOGICAL MANIFESTATIONS[1]

By Frederick Tooke

(From the ophthalmological service of Professor J. W. Stirling)

In considering the question of the miliary choroidal tubercle, in spite of the recognition of an extensive expression of opinion on that small pathological lesion, one is almost discouraged at one's first investigations by the varied findings of the several authorities. No less is one astonished at those who have overlooked a more complete reference to this important detail in the general treaties on tuberculous cerebro-spinal meningitis. Bramwell, in Osler's *System of Medicine*, 1910, volume vii, dismisses the question with the statement that choroidal tubercles, when present, make the diagnosis certain. He states that Koplik found choroidal tubercles in 9 of 46 cases in the first two days of illness. Batten, in Albutt's *System of Medicine*, supplies one with a little more information, and says that ophthalmoscopically the two changes which require consideration in the disease are optic neuritis and choroidal tubercles, to which, respectively, attention was first directed by Albutt and by Cohnheim. With regard to optic neuritis, Batten states that its indications in the early stage of the disease are often ambiguous, but late in the disease it can generally be detected on both sides, though unequally. Even then it is rarely severe or comparable with that associated with cerebral tumour, but the increase of blurring of the edge and of curving of the vessels is conclusive to one who has observed the progressive change in a given case.

In judging of the progress of the neuritis, Garlik lays great stress in these cases on the alterations which take place in the

apparent lumen of the arteries and veins, and on their altered
relation to one another. Batten further states that tubercles
of the choroid can be observed occasionally in successive devel-
opment at the various parts of the fundus, beginning as minute
round dots, which gradually become opaque in the centres and
sometimes confluent at the margins. Tubercles of the choroid
that seem to develop during the course of a brain illness are so
far in favour of that illness being tuberculous meningitis. He
found that out of 16 consecutive cases of choroidal tubercles,
13 showed post-mortem evidence of tuberculous meningitis,
while 3 presented tubercles in other organs, but no tubercle in
the pia mater. Thus, apart from any other sign, tubercles of
the choroid cannot be taken as indicating that there is neces-
sarily a deposit also in the pia mater, but it bears witness to
a widespread tuberculosis.

Marple, in an article read before the Congress of Ophthal-
mology at Oxford, in 1912, made the assertion that tubercles
are to be seen in every case of tuberculous meningitis. In
Gower's work on *Medical Ophthalmoscopy*, in which one
must at once associate the collaboration of the late Marcus
Gunn, the statement was made that tubercles of the choroid
may now and then be found in tuberculous meningitis. Cohn-
heim would have us believe that these tuberculous bodies are
less frequent in tuberculous meningitis than in generalized
tuberculosis without meningitis. In contradiction to Marple's
findings, Heinzel, after examining 41 cases of tuberculous
meningitis, was unable to convince himself that tubercles were
present in a solitary instance; while Garlik, after repeated
examination of 26 cases, was satisfied with their presence in
only a solitary instance.

Again, Marple's figures are supported in part by the find-
ings of Carpenter and Sydney Stephenson, who are satisfied
that they are present in 50 per cent. of the cases, while further
evidence is attached by the figures of Bock, who places the
percentage at 82.7 and Leiter at 75.

So much for conflicting evidence by way of an introduc-
tion.

There is no doubt in the mind of the writer that much facility in examining the fundi of these cases has been afforded by the various patterns of electric ophthalmoscope at present in use, allowing at once more frequent examinations with a minimum amount of effort, as well as bringing out more brilliantly illuminated details of the interior of the eye. Yet, on the other hand, one cannot but feel that such brilliancy of illumination, even with a frosted globe, produces strong light reflexes thrown by the filaments of an electric lamp as well as those cast by the walls of the vessels on the retina, and which produce erroneous impressions on the mind of the observer. These impressions of such minute lesions one is apt to interpret as pathological lesions. In my examinations I have consequently tried to avoid such possible fallacies where opportunities were favourable, and have used the electric ophthalmoscope in conjunction with the less brilliant but possibly less disguised picture of a reflected image with a Morton instrument.

In the early stage of the disease, where much restlessness and opposition to examinations are displayed by the patient, and where an examination of the fundi is rendered more or less difficult, the electric ophthalmoscope is a manifest advantage. In my experience, however, as my figures will subsequently show, findings of any importance are generally not noted during the period of incubation, but rather toward the end of the disease. In spite of convulsive spasms which may ensue shortly before exitus, much less actual resistance is met with. The method generally employed is to place a clean towel or a piece of gauze over the lower half of the patient's face, in order to render a rather unpleasant examination as hygienic as possible when adopting the direct method. In cases toward the end of the disease, where exfoliation of the corneal epithelium has begun, I have a saline solution applied to the eye by an assistant, from a small drop bottle. I have used this method also very shortly after death, before colloid changes have occurred in the vitreous, in an endeavor to define possible tubercle formation which I could not satisfy myself existed up to the time of death. Although it is frequently unnecessary,

a drop of atropine is instilled into each eye every couple of days in order to facilitate the examination.

I have considered myself fortunate that my efforts in an investigation on this subject have been able to be carried out in the wards of a large general hospital. Many of the authorities whom I have quoted have based their statistics on examinations made in children's hospitals. Although a recognized eye hospital is a desideratum in every community, yet it cannot be denied that a properly equipped and conducted eye clinic in a general hospital will frequently afford opportunities for special study of the fundus oculi requisitioned from other services. It may consequently be interesting to know that from the figures which I have collected from the records of the Royal Victoria Hospital, Montreal, tuberculous meningitis is far from being confined to childhood. It is quite true that young children form a fairly large proportion of all cases, but the disease, as generalized tuberculosis itself, may be present at any age. I have seen cases of tuberculous meningitis in the fifth and sixth decade, where rather obscure conditions clinically were finally cleared up post-mortem, and in one case, at least, where a definite clinical diagnosis was established only by the detection of choroidal tubercles with the ophthalmoscope.

In 102 cases which I have collected there were 60 male and 42 female patients. The ages of these patients may be classified as follows:

Between 1 and 2 years............ 7
" 2 " 5 " 23
" 5 " 10 " 15
" 10 " 15 " 12
" 15 " 20 " 14
" 20 " 30 " 15
" 30 " 40 " 9
" 40 " 50 " 2
" 50 " 60 " 5

It is a matter of regret that of these only 73 were referred from the Department of Internal Medicine to the section of

Ophthalmology. Regarding the condition of the fundus oculi, the findings are, in consequence, less complete than had a routine examination been made by a competent authority in each individual case. A few cases are recorded both of negative and positive findings by medical house officers, but most of us who have served in such capacity in our early experience know and readily admit that our skill and reliability are hardly commensurate with our good intentions in an examination of this nature at this particular period.

Of the 73 cases examined by members of the attending staff, choroidal tubercles were present in 7 cases. In every instance they appeared not earlier than three days before death. In one case repeatedly and separately examined by each member of the attending staff, the mere suggestion of a solitary tubercle formation was first noted by the writer three hours before death. This condition was verified post-mortem, and I am privileged in being able to demonstrate sections of the eye from this patient (Fig. 1).

Only too frequently, however, cases have been examined but once or twice at what one might consider a considerable interval of time before exitus, with negative findings regarding the presence of tubercles. It is further to be regretted that many of these cases were not followed more frequently. In a number, however, which I have been privileged to study, I have followed them up to within three or four hours prior to death, feeling that tubercles might appear as a final manifestation. The two cases which I have examined in the last month—one six hours and the other three hours before death—in each case there was present a slight degree of perineural œdema, as I have generally noted in cases with an actual tuberculous formation, but in these two cases up to that time tubercles were not present. In these cases, as in others examined late in the course of the disease, and where I had felt a certain degree of misgiving and discouragement regarding my ophthalmoscopic findings, I followed them to autopsy only to have my clinical report substantiated.

It may be held that these tubercles have a peculiar faculty of evanescence, manifesting themselves clinically, only to disappear prior to death. Although allowing that fresh tubercles may possibly make their appearance, and perhaps even that some may vary in size and position, it has been my pathological experience that cases which I have seen and the sections which I am showing in this contribution correspond exactly post-mortem to the ophthalmoscopic findings.

Early inflammatory changes about the nerve, described by some as perineuritis, by others rather as a perineural œdema, were recorded in 30 cases of the 73 examined. This manifestation was reported varying from five days to one day before death, and when present, the tubercles of the choroid were invariably an antecedent to the latter condition. Changes of this nature I have generally found to be associated with conditions of a basal type of meningitis, where the disease progressed forward to the optic chiasm, frequently following the sheath of the cranial portion of the optic nerve up to the sphenoidal fissure (Fig. 2).

Regarding the presence of choroidal tubercles, could our experience be that of Marple, or even that of Carpenter and Stephenson, it might be held as a strong point in the diagnosis of many obscure cases. That they have been shown to be absent in many cases post-mortem, with active tuberculous lesions in the meninges, would offset their diagnostic value as a negative factor. In adult cases their presence may shed light on what has been regarded as an obscure condition.

PATHOLOGY

Regarding heredity as an etiologic factor, it is absolutely useless to discuss.. In a number of cases it is true that a clear and definite family history of tuberculosis could be elicited, and in many instances was candidly admitted. In many cases of foreigners, particularly those of Jewish extraction, who, by the way, constituted 21 per cent. of the total number, where very intelligent information could not be obtained relative to

their prior health and to that of their progenitors, it was absolutely impossible to have any of them admit of being victims of any of the ills that flesh is heir to. This may be attributed to ignorance or to the unnatural caution and suspicion of such a class.

It is not the intention of the writer to attempt to present anything resembling a complete treatise on the general pathological lesions found in tuberculous meningitis. Such a course would be far from the original idea of this paper. Incomplete post-mortem examinations were made in 48 cases, and of these 38 included the head, while in 5 cases permission was refused that most important part of the anatomy for study and observation. I may say at the onset that there was no case of tuberculous cerebro-spinal meningitis without other manifestations of tuberculosis elsewhere in the body. There was, further, no such case as a primary miliary tuberculosis of the meninges.

To enumerate the foci of coincidental lesions would be to include the whole human organism. As in the case of tuberculous lesions in general, so in this particular manifestation of a general disease, evidences were most frequently found in the lungs; in fact, in no isolated case where a general post-mortem examination was performed, not even in early childhood, was the chest cavity found to be free from tuberculous disease. One case in particular, suggesting a hæmatogenous nature of the infection, showed an old tuberculous focus in the lung which had relighted and had broken directly through the wall of one of the pulmonary vessels. It has been rather interesting to note co-existing manifestations of ulceration in the large or small bowel in 17 per cent. of the cases.

A description of the usual pathological findings of a case of meningitis due to tuberculous diathesis is, as I have already said, made unnecessary. But I will confine my remarks to a few of the commoner lesions which were recorded about the base of the brain. Changes of a pathological nature directly involved the base of the brain in so far as one could determine, microscopically speaking, in all but two cases. In these two

exceptions no fundal changes were noted. As a rule, the brain was inclosed in its meningeal sheath in a turbid, greenish, grayish fluid, which frequently assumed a fibrogelatinous appearance at the base of the organ. This fluid differed distinctly in its post-mortem appearance from that obtained from lumbar puncture prior to death, where it, as a rule, appeared perfectly clear.

Miliary tubercles were noted in varying numbers, sometimes very few, but when present they were localized toward the base. When the structures at the base of the brain were involved, it is interesting to note the number of miliary tubercles which seemed to have a predilection for the fissure of Sylvius. Tubercles at the base varied in size, also in position, from the sheath of the cranial portion of the optic nerve forward, to the cerebellum behind. In one case a tuberculoma of the right optic nerve was present, and the eye exhibited a well-defined perineuritis, as well as a small solitary tubercle of the choroid, after very late clinical manifestations (Figs. 1 and 2). Two cases of coincident tuberculoma of the cerebellum with basal manifestations of miliary tuberculosis had not shown any unusual signs in the fundi prior to death. In those cases which were sufficiently extensive to include the vessels at the base of the brain, it was interesting to note how frequently these were studded along their course by these small miliary bodies. Direct reference has been made to them in almost half of the cases, and with fundal changes occurring in many of them it must suggest a hæmatogenous source of infection in the case of the tubercle at least. Their appearance, however, does not mean that perivascular tubercles had of necessity to be responsible for the presence of changes in the fundi, for it is worthy of note that, in a number of instances where such post-mortem changes were remarked upon, negative reports had been made of the fundus only a short time before death occurred. It consequently seems that these changes in the fundi are, in all likelihood to a very large extent, due to a hæmatogenous infection. At the same time it is quite impossible to exclude sources of infection by way of the perivascular

lymph-spaces, as certain of my sections would seem to point out. Von Græfe has stated that the optic neuritis found in tuberculous meningitis is a descending one, and due to a direct extension from the pia-arachnoid space through the trabeculæ of the optic nerve, setting up direct inflammatory changes. In the 30 cases manifesting changes about the optic nerve there was only one on record which showed anything at all resembling a high degree of inflammation, the changes being rather those of venous engorgement with perineural blurring about the margins of the disc. I have never seen in any of these cases a choked disc of measurable swelling. My explanation for such clinical findings is that the changes about the optic nerve are not altogether through the trabeculæ of the optic nerve and along the course of the nerve-fibres, as certain authorities would have us believe. In the cases to which I have already referred, where a tuberculoma existed about the cranial portion of the sheath of the right optic nerve, the condition was further involved involved by the presence of innumerable tubercles. Sections through this portion of the nerve show an absolute caseation involving all sheaths of the nerve, with an intense infiltration completely occupying the space between the nerve and its sheath, as well as following its ependyma. This condition was confined to that portion within the cranial cavity over which the tubercles are situated (Fig. 2). That portion without the cranial cavity and within the orbit shows no such similar microscopical appearance, this seemingly having been arrested in the neighborhood of the sphenoidal fissure. There is, consequently, no such condition as direct filtration through the vaginal space. The orbital portion of the optic nerve shows there is direct infiltration of the pia-arachnoid but nothing more. Such an intense condition as that found within the cranial cavity is nowhere noted, and nothing at all resembling caseation occurs. In fact, tubercle formation is not present The tiny vessels of this portion of the optic nerve sheath, however, are frequently engorged, and one can distinctly, in a number of instances, make out in the vaginal space tiny capillaries showing an egress of lympho-

cytes through their walls to be possibly thrown free into this space or to constitute the nucleus of subsequent perivascular tubercle formation (Fig. 3).

Regarding the structures of the choroidal tubercle itself, I have found that they vary somewhat in size from 0.5 to 2 mm., the smaller ones generally being the more common. They are generally found, in my experience, in the posterior hemisphere, and, as a rule, near the bifurcation of one of the larger retinal vessels. The first manifestation of a tubercle involving the choroid is that of a tubercle elsewhere; engorgement of a vein or of a small capillary through which a subsequent migration of lymphocytes occurs. From this procedure there is constituted a condition of perivasculitis which in due time encircles the whole lumen of the vessel (Figs. 4 and 5). Following this perivascular infiltration of lymphocytes, changes occur in the blood-vessel itself, which may vary as follows: in the first place, it may merely be strangulated by the pressure of its encircling zone of inflammatory change, at the same time cutting off all nutrient supply to the vessel itself; in the second, a hyperplasia of the media may have a great deal to do with excluding its lumen; and, finally, an endarteritis obliterans may ultimately close up this whole focus from subsequent blood-supply.

With the infiltration of lymphocytes there occurs a coincident infiltration of fibroblasts; and, no doubt, should the lumen of the vessel become completely occluded, caseation would in due course ensue. Although some of my sections show such vascular processes well on toward completion, yet in no instance was I able to determine that they were such as to show actual microscopic changes, although I believe that such changes have been noted by other observers. This condition would naturally be noted in cases where tubercles had made an early clinical manifestation, rather than in those which I am showing, where they appeared later on in the disease. Histologically speaking, death of the individual probably precedes that of the tubercle.

Giant-cell formation is typically shown in two cases without there being of necessity a process of caseation. Tubercle bacilli have been noted in several instances, but, being of a rather frugal mind, I have preferred to preserve my rather scanty material for the preparation of sections and to accept the statement and manifestations of the sections provided by my friend, Dr. Brown Pusey, to whom I wish to record my sense of appreciation. It is interesting to note, in regard to the formation of miliary tubercles of the choroid, how closely they are confined to the vascular elements of the eye. In every instance which I have so far seen, the infiltration never seems to have gone beyond the region of the choroidal bloodvessels, the pathological process being invariably included within the delicate hyaloid membrane of Bruch on the one hand, and within the scleral coat on the other. I have never seen the slightest evidence of infiltration between the membrane of Bruch and the retina (Fig. 6).

Regarding the pathology of cerebro-spinal fluid, this, in my opinion, may be accepted as a much more reliable source of information for the establishment of a clinical diagnosis. In all cases a definite leukocytosis was present, the lymphocytes being invariably in the ascendant. One case, however, was rather misleading, polymorphonuclears being more numerous than the lymphocytes, in the proportion of 70 to 30 per cent. In another case they were equally divided, but both cases show definite pathological lesions at the base of the brain, as well as elsewhere in the body, of a distinctly tuberculous nature. In the vast majority of cases, however, the proportion of lymphocytes was well over 75 per cent., and in more than one case rose as high as 100 per cent. The degree of lymphocytosis would not appear to have any direct relationship to co-existing manifestations in the choroid or the optic nerve.

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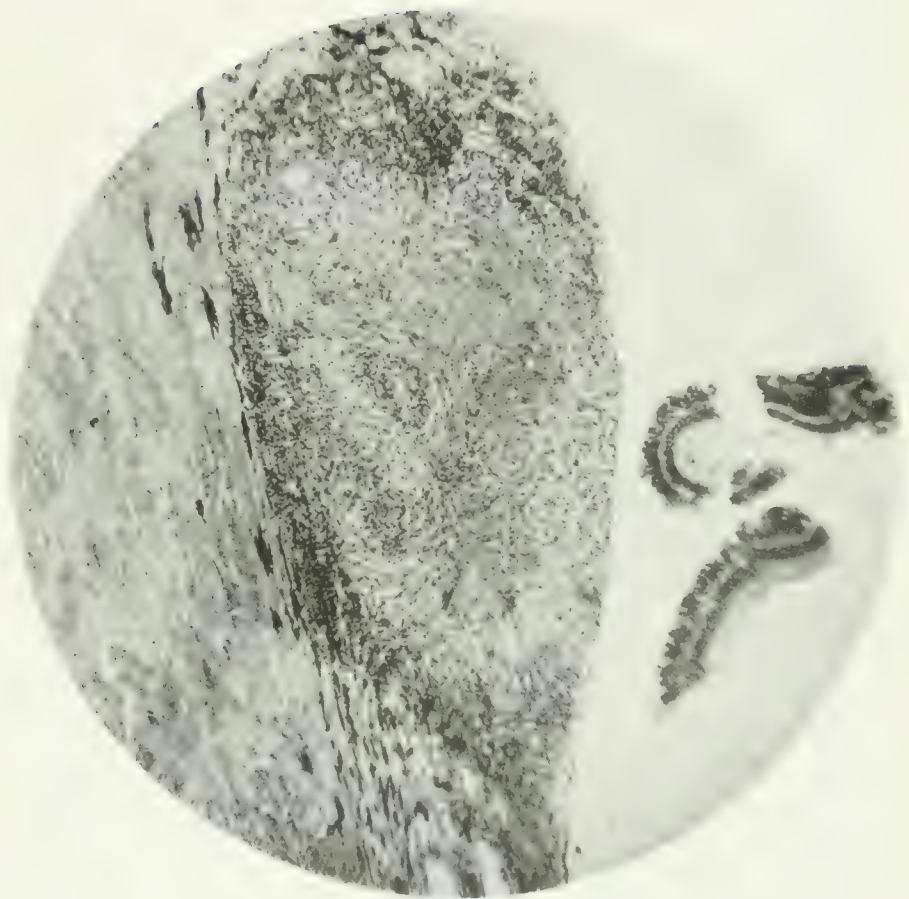GREEFF.   *Orth's pathologische Anatomie,* 1903, part x, p. 312.

Fig. 1.—Female patient, aged eighteen. First manifestation appeared twenty-four hours before death as a tiny, pin-head point of hyperemia, less diffuse at its periphery. Definite tiny, pearl-gray body replaced it three hours prior to death. Section shows gradual occlusion of choroidal bloodvessel, with circumscribed infiltration of lymphocytes and an intervening area of fibroblasts which appear to be approaching the stage of caseation.
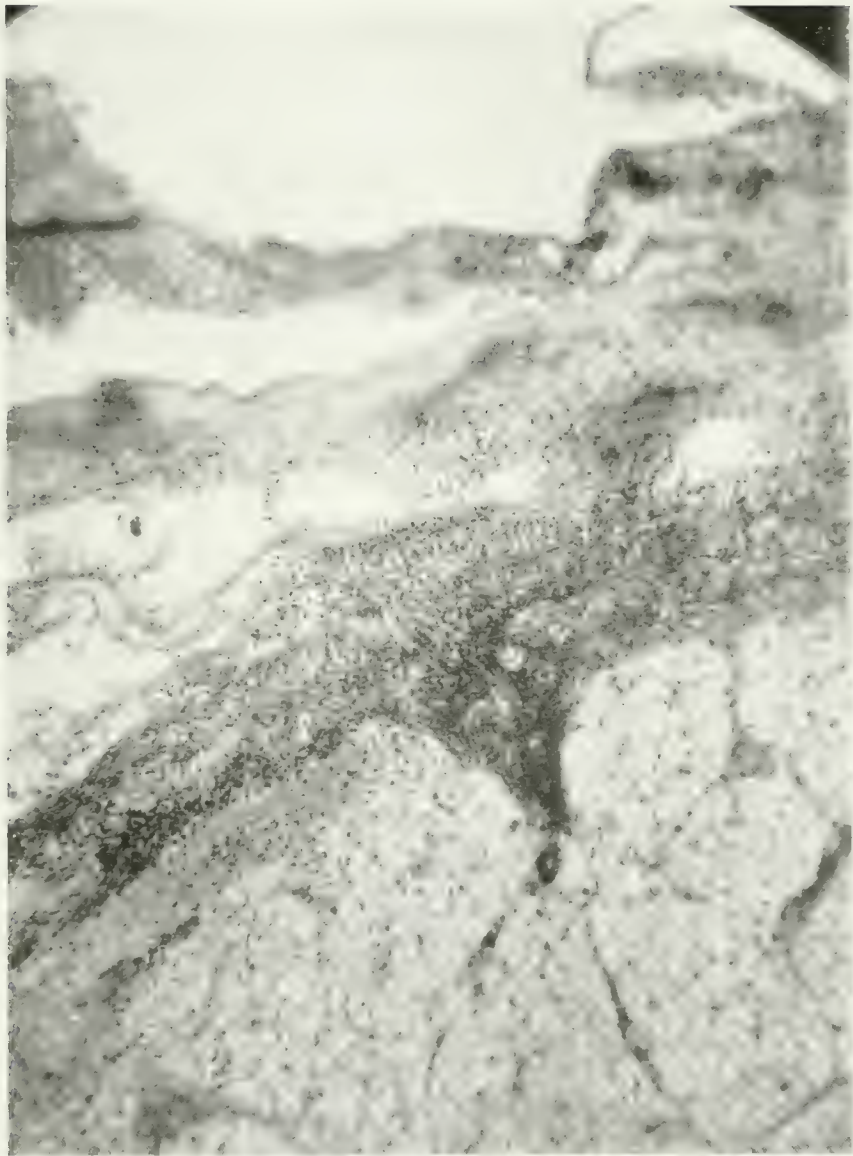
FIG. 2.—Same patient as Fig. 1. Section of intracranial portion of optic nerve near sphenoidal fissure. Clinically a slight degree of perineural blurring was noted. Sheath of optic nerve studded with innumerable miliary tubercles, which at one point coalesced to form a tuberculous granuloma. Separate layers of optic nerve-sheath included in one granulomatous mass. Dense infiltration of leukocytes between sheath and optic nerve itself, with infiltration along trabeculæ of optic nerve. No giant-cell formation.
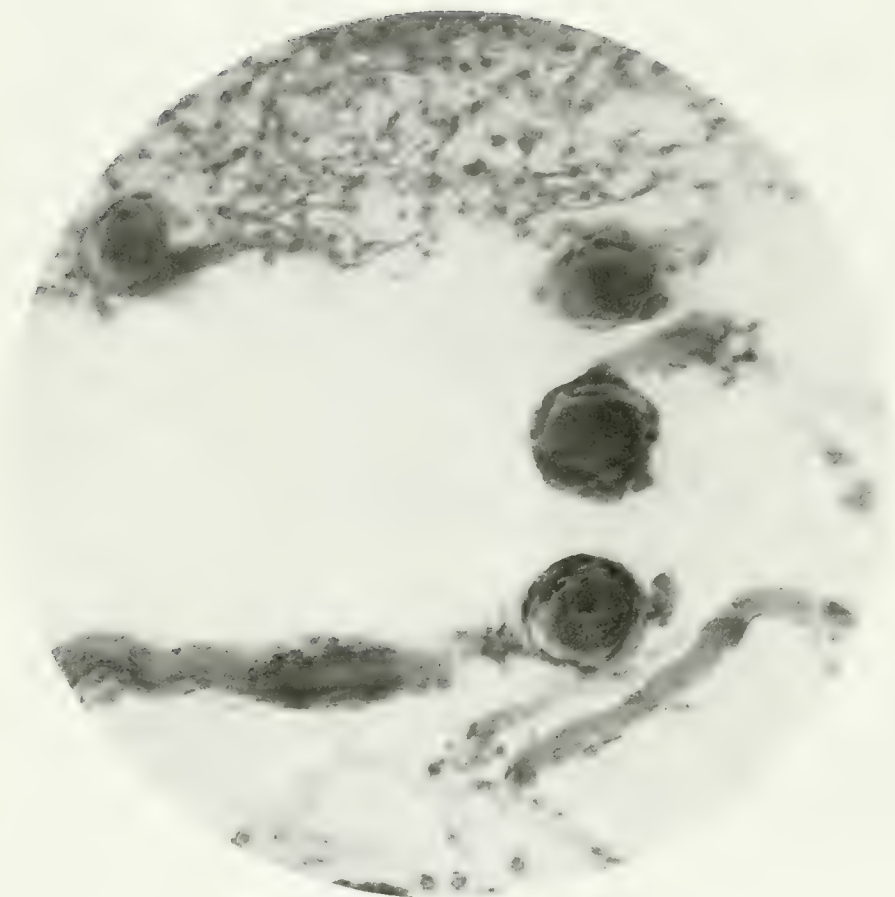
FIG. 3.—Section from same patient as Fig. 2. Orbital portion of optic nerve close to eyeball. Clinically a slight condition of perineural blurring was noted. Slight infiltration of pia-arachnoid coat of nerve-sheath, with very moderate infiltration of leukocytes from it into vaginal space, as contrasted with cranial portion of nerve. Tiny blood-vessels distinctly engorged with transudate of lymphocytes through vessel-wall, the nuclei of perivascular tubercles.
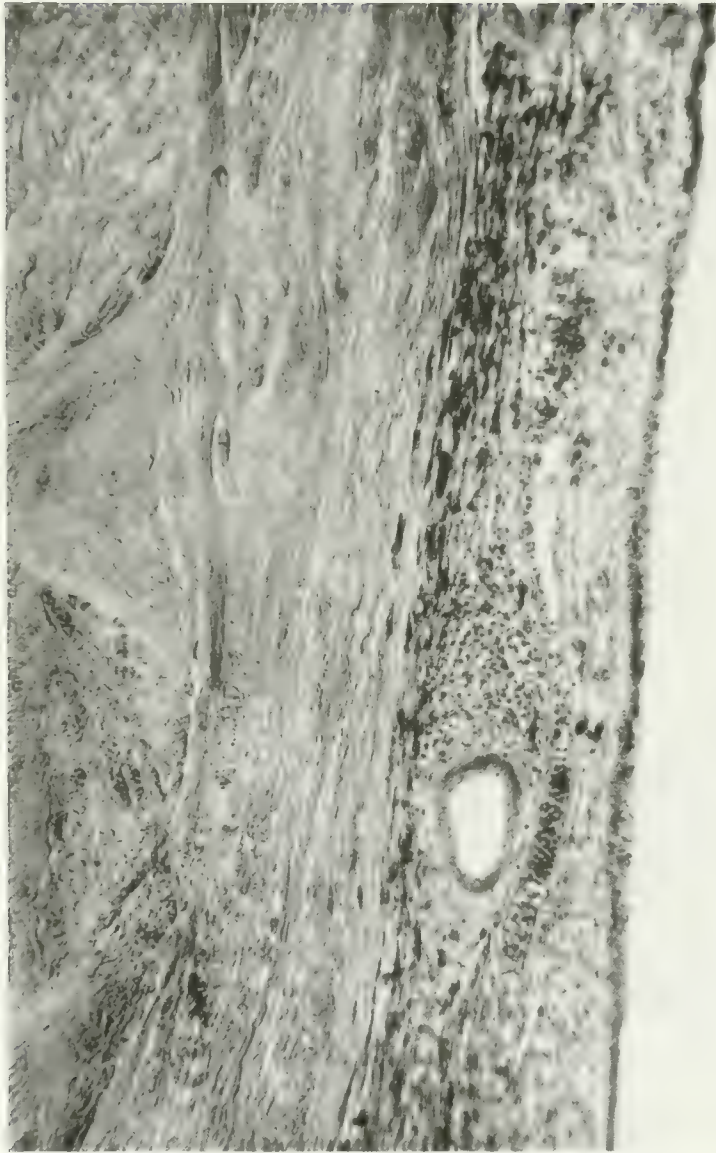
FIG. 4.—An early pathological manifestation of a tubercle of the choroid. Engorged choroidal capillary, with exudate of leukocytes through vessel-wall. Dilated blood-vessel, which is showing a condition of perivasculitis of a fairly advanced degree.
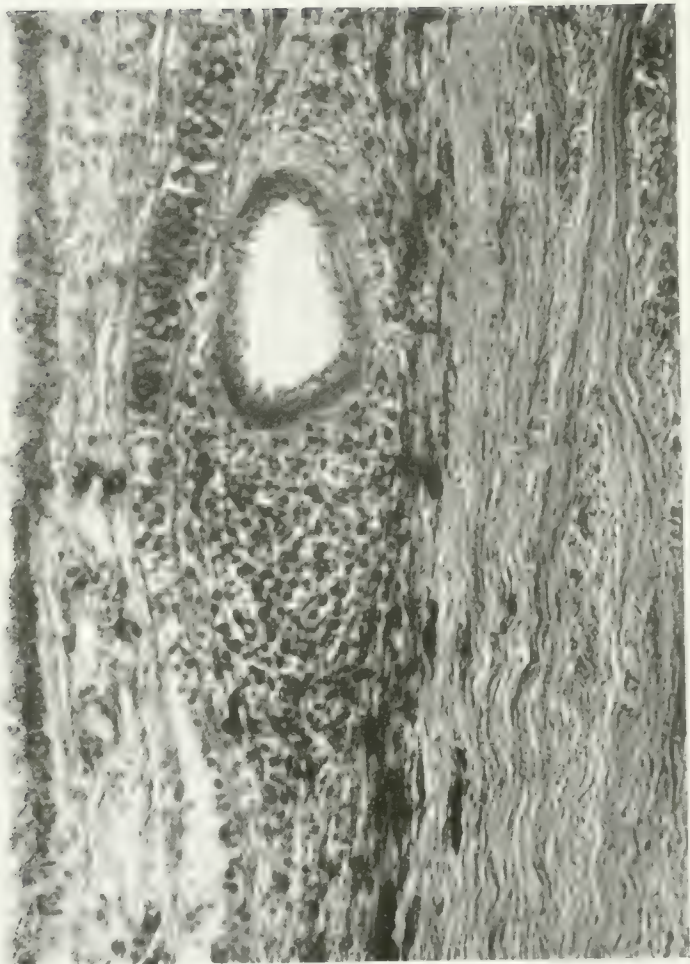
FIG. 5.—Same as Fig. 4, only higher magnification. Section clearly shows egress of lymphocytes through the capillary wall, forming the zone of perivasculitis or infiltration about a dilated vein.

FIG. 6.—Male patient, aged seventeen. Tubercle first noted clinically twenty-four hours before death. Tubercle confined entirely to choroidal coat, and consists of a peripheral zone of infiltration in which are included fibroblasts, through which are scattered numerous giant-cells. Caseation has not occurred to any appreciable degree. The pathological lesion is confined entirely within the membrane of Bruch, and does not extend backward from the choroid to the sclerotic coat.

FACIAL PARALYSIS ASSOCIATED WITH ACUTE SUPPURATIVE MASTOIDITIS CURED BY MASTOID OPERATION

By D. H. Ballon

(From the oto-laryngological service of Professor H. S. Birkett)

Case 1.   J. L. B., male, age 33.   Manufacturer.

History

April 20, 1915, at R.V.H., I did a radical mastoid operation on the right ear for Chronic supp. ot. Media. of 14 years duration, which prior to admission had developed a labyrinthine fistula.   On May 6, 1915, while blowing his nose, the patient heard "something crack" in the left ear and on the next day there was a profuse, purulent, painless discharge which persisted.   The pus would well up out of the ear in spite of the fact that it was syringed every two hours.   There was, of course, deafness, but no fever or mastoid tenderness.   The drum was slightly swollen posteriorly and pulsations were visible.   On May 22nd, paresis of left facial nerve developed; a paracentesis was immediately done.   May 24th, there was no improvement; mastoid tenderness was present over the antrum, emissary vein and tip.   There were occasional shooting pains on the left side of the head.   The X-ray confirmed the diagnosis of acute mastoiditis.   May 27th, simple mastoidectomy was performed.   When the cortex was removed abundant pus under tension was found.   The pneumatic spaces were broken down and filled with pus and granulations. All disease tissue was removed, and free drainage was established.   The latera sinusi and dura were not exposed.   The wound was packed with iodoform gauze.   On May 31st, gauze removed; the middle ear was dry, the facial paresis had almost

disappeared. The patient was up and about the ward. July 6, 1915, mastoid wound healed; hearing excellent. Facial paralysis completely cured.

CASE 2. B. M., age 37. Butcher.

HISTORY

January 28, 1916. Two months ago, following a cold in the head, the patient became deaf and had a profuse purulent discharge from the right ear. There were no other complaints until three weeks ago when, as a result of an acute exacerbation of the cold, he began to have severe violent throbbing pain in the same ear radiating along the right half of the head, keeping him awake at night, and compelling him to seek relief in a hospital at three A.M. With the onset of the pain the discharge from the ear diminished. At the same time he suffered from frontal headache, fever, anorexia, and occasional dizziness. There was no vomiting, chills, sweats, or ataxia. Ten days ago he noticed that he could not close his right eye, whistle, or masticate his food properly. Three days ago a swelling appeared below the lobule of the right ear.

On examination there was very little non-fetid discharge from the right ear. The drum was congested, swollen posteriorly, and pulsations were visible. Hearing—loud speech was limited to contact and he gave the usual tuning fork tests for acute suppurative otitis media. There was no nystagmus, Barany's pointing test was normal, and the caloric reaction was present. No fistula symptom. In the mastoid region there was a large brawny, indurated, markedly tender but non-fluctuating swelling between the tip of the mastoid and the angle of the jaw, extending also along the side of the neck behind the sterno-mastoid; the head was fixed. There was tenderness over mastoid and emissary vein The case was seen by Doctor Mundie, who found complete paralysis of the facial nerve including the chorda tympani. X-Ray showed the right mastoid somewhat sclerosed and cloudy. The lateral sinus was distinctly visible.

On January 26, 1916, at R.V.H., simple mastoidectomy was performed. The mastoid was completely exposed; no perforation could be found either at tip or near the antrum. After removing the sclerosed cortex the pus swelled up under pressure. A perisinus abscess was found and with every pulsation of the lateral sinus pus appeared. There was no thrombosis. The sinus was very far forward, about half an inch from the mastoid antrum. The mastoid cells were very extensive, and pneumatic and filled with pus and granulation tissue. All the diseased tissue was completely removed until healthy bones was present everywhere and free drainage was established with the middle ear. The mastoid tip was removed but no pus was found in the digastric fossa. The infiltrated mass at the side of the neck was drained and packed with iodoform gauze. Cultures of the pus were examined by Doctor A. A. Bruère, who reported a hæmolytic streptococcus. On January 31st, patient was up and about the ward. February 12th, discharged. The facial paralysis had considerably improved; he could partly close the right eye. February 21st, patient was able to whistle. March 10th, facial paralysis had almost completely disappeared so that he required no further electrical treatment. The hearing was perfect.

CASE 3. L. P., male, age 1 year, referred by Dr. Tannenbaum.

HISTORY

March 13, 1916. Two weeks ago the child had tonsilltis, one week later he developed a cough with a temperature of 102 and a nasal discharge; about this time a swelling appeared behind the left ear. No aural discharge. On examination there was a small, round, tender, glandular, retroauricular swelling. Apart from a slight opacity the drum was practically normal. In a few days, by the use of an ice bag, the swelling disappeared and the temperature dropped to normal. The next time I saw the patient was on April 5th, when he had a complete facial paralysis on the left side. At no time was

there ever a history of a running ear.   The drum was opaque, the outlines indistinct, and there was no bulging.   A paracentesis was done; the next day a slight aural discharge appeared. There was no fever, but mastoid tenderness behind the left ear in the region of the antrum.   On April 16th, at the R.V.H., a simple mastoidectomy was performed.   The whole mastoid was extensively diseased and filled with pus and granulations. All this was removed and free drainage established with the middle ear.   April 9th, discharged.   By the middle of June the paralysis had completely disappeared.   It is to be noted that in this case infection of the mastoid was undoubtedly by direct extension from the middle ear.   The latter had evidently healed up very quickly, thus preventing free drainage from the mastoid.

Etiology of Otitic Facial Paralysis

In this report we are only considering facial paralysis which is caused by some acute middle ear or mastoid disease. The condition is by no means common, and is found more in children than in adults.   Influenza, scarlet fever, and severe infections are the most frequent causes.   Its onset may be gradual or sudden, involving either the whole or a portion of the nerve, and it is always present on the same side as the ear affected.   The facial paresis or paralysis is produced by an inflammation of the nerve in its passage through the middle ear.   From the latter the severe inflammation process extends and erodes the tympanic wall of the Fallopian canal, either directly involving the nerve or else subjecting it to pressure from the inflammatory exudate within or without the canal. There may of course be only a mild perineuritis or neuritis. Occasionally the seventh nerve is involved through a defect or dehiscence in the tympanic wall of the facial canal.

Prognosis and Treatment

The prognosis is very favourable under prompt and rational treatment.   Operate immediately with the appearance of the facial paralysis resulting directly from middle ear or mastoid

suppuration. Remove all diseased bone and granulations. Establish free drainage by a simple mastoidectomy or radical mastoid according to the nature of the tympanic lesion. Even before the mastoid operation is performed, a paracentesis should be done to relieve the tension in the middle ear. The prognosis is naturally influenced by the cause, duration, presence or absence of muscle degeneration. If actual division of the nerve has occurred, permanent paralysis will result unless the segments are reunited. If paralysis is due to pressure, then the prognosis is good providing the drainage is free and early effected; if due to necrosed bone, much will depend on the possibility of removing the existing bone lesion and how much damage has already been done to the nerve. In the early stages of facial paralysis the electrical reaction of the facial muscles is diminished; if there is no response to Faradic stimulation the outlook is grave. To prevent atrophy of the facial muscles daily massage and electricity should be instituted as early as possible Strychine sulphate gr. 1/60 T.I.D. over a considerable period has been advised, but its influence is open to question.

The writer is indebted to Dr. G. S. Mundie for making the neurological examinations and carrying out the necessary electrical treatment.

CONTRIBUTIONS TO THE PATHOLOGICAL ANATOMY OF THE PANCREAS

(From the pathological laboratories)

I

ON CERTAIN CHANGES IN THE PANCREAS IN DIABETES MELLITUS AND THEIR POSSIBLE RELATION TO NORMAL PANCREATIC EVOLUTION

By Horst Oertel

After reports of pancreatic disease in diabetes mellitus had been made from the latter half of the eighteenth century (1788) (Cowley) to the latter half of the nineteenth century, Lanceraux stated definitely in 1880 that a general relationship existed between *diabète maigre* and affections of the pancreas, while *diabète gros* depended upon other constitutional factors such as gout, obesity, etc. These observations were extended by Cantani and Ferraro, who in the following year demonstrated fatty degeneration and atrophy of the pancreas in five histologically carefully studied cases. A pathogenetic explanation of these changes and their relation to diabetes mellitus was attempted by Hoppe-Seyler in connection with report of a case in 1894. In this instance only small pieces of pancreatic tissue were found preserved between masses of fat in the pancreas of a woman of 57 years who had died in diabetic coma. Histologically even these pieces showed alterations: around the ducts the connective tissue was markedly thickened, the cells stained poorly, the glandular lobules were atrophic, surrounded by connective tissue and partly replaced by connective tissue with fat, arteries much thickened and narrowed, veins wide. Hoppe-Seyler regarded the lesion as the result of advanced arterio-sclerosis leading to nutritive disturbances in the pancreatic parenchyma, connective tissue hyperplasia and fat

infiltration, essentially similar to arterio-sclerotic changes in the kidney, and held that when the process in the pancreas reaches a certain degree the organ looses its function and fatal diabetes results. In the same year appeared Hansemann's extensive publication on the subject. Hansemann contrasted the diabetic atrophy of the pancreas, which he termed "genuine granular atrophy" and which he regarded as specific for diabetes, with other, accidental, atrophies which are only occasionally associated with diabetes. He regarded the genuine granular atrophy as a chronic interstitial inflammation. It is, in his opinion, associated with general functional loss from the very start. Like Hoppe-Seyler, he compared it to genuine contracted kidney and, as stated, quite specific for diabetes. He considered that other, or accidental, atrophies only lead to diabetes when loss of parenchyma exceeds certain quantitative limits.

These views were modified and largely changed by certain observations recorded first in an inaugural dissertation, in 1894, by Dieckhoff (Leipzig) who described seven cases of diabetes and found in one loss of islands of Langerhans and in another various chronic, rather indefinite, changes. But it was especially after Opie's work, and that of some others, that the attention became centred around the islands, and glandular changes were neglected, or received, at least for a time, much less recognition. The history of this research is too well known to be reviewed once more, but it is sufficient to emphasize that various investigators have during recent times attempted to rehabilitate the importance of the *whole* pancreas in relation to diabetes and to deny the physiological and pathological specificity of the islands. Reitmann and Herxheimer, more particularly, have revived and somewhat modified the ideas of Hansemann and speak of a "cirrhosis pancreatica diabetica." Reitmann's article is especially noteworthy as an extensive, valuable study of normal and pathological pancreatic conditions and will be referred to in this regard later. In diabetes he compares the pancreatic disease to cirrhosis of the liver in so far as the atrophic, degenerative, interstitial and regener-

ative changes lead to an entire reconstruction of the organ. (Similar to Kretz's observations and views of liver cirrhosis and my own in the contracted kidney.)

Several years ago I had an opportunity to study the markedly atrophic pancreas of a young man of 33 years who had died in diabetic coma and which showed changes different in many ways from those described above. In this case the gross and microscopic atrophy occurred without cirrhosis or marked fat infiltration, but it had led a remarkable collapse of pancreatic structure. Acini were lost or visible only as faint remains or exceedingly small. Their place was taken by a rather diffuse aggregation of, for the most part, small polyhedral, more or less undifferentiated cells, irregular in shape and size, evidently derived from desquamated and atypically regenerating parenchyma cells. Islands were no longer visible. This pancreas resembled closely that of a cat ten days after ligature of the pancreatic duct in a very similar collapse of pancreatic structure, except for a greater connective tissue proliferation between the atrophying lobules after ligature. (See Milne and Peters, *Journal of Medical Research*, vol. xxvi, No. 3, July, 1912, Atrophy of the Pancreas, etc., where an illustration of this diabetic pancreas will be found.) During the last year I have had a further opportunity to study the pancreas in three cases of severe diabetes, all of whom died in coma. The changes which these present were of a similar nature, and represent in my opinion only stages of one and the same process. The closest similarity existed between the last case of this series and the one observed several years ago. Grossly all three showed marked general pancreatic atrophy without cirrhosis and fat infiltration. I quote the protocols:

1. A187–14. Male, age 32. Death in diabetic coma. Duration of disease 15 months.

Pancreas weighs 35 grm., small, short, rather narrow, lobules small, pale, no fibrosis, not fatty, no vascular thickening. Microscopic examination: *parenchymatous atrophy;* lobules are small and widely separated by thin fibrillar tissue. No fat infiltration. Acinar glandular tissue shows all grades

of atrophy; generally the acini are small, some extremely so. They lie in close proximity, and sometimes the acinar arrangement becomes indistinct, almost obliterated.

In the markedly atrophic districts the cells are small, their outlines indistinct and the number of cells in the collapsing acini usually diminished to few, but their nuclei and protoplasm usually stain well and the latter is smooth or granular. In contrast to these are lobules in which the pancreatic structure is much better preserved and defined in its acinar arrangement, and these acini and cells appear rather large in contrast to the atrophic parts. But even in such lobules irregularity in size of acini is noticeable, and large and small alternate. Definite islands cannot be recognized but various transitional pictures are seen. Bloodvessels and ducts are not thickened.

2. A56–15. Female, age 32. Death in diabetic coma one week after admission. Duration of disease indefinite. Pancreas is small, firm, and measures 14.5 x 3.1 cm., and shows no gross lesions. (Weight not given.)

Microscopically: *Atrophy and partial collapse with irregular atypical cell increase of parenchyma:* marked atrophy, particularly in the centre of widely separated lobules. Acini show all stages of atrophy to collapse are often poorly outlined and in close proximity. The cells themselves are generally atrophic, indistinct, poor in outline, not much larger than lymphocytes, round, occasionally polygonal, and frequently contain several dark nuclei. In other parts occurs marked, almost diffuse, increase in nuclei and in undifferentiated cells with irregularity in size and shape of acini, some appearing hypertrophic and tortuous, their lining occasionally syncytial and the protoplasm deeply chromatic (Fig. 1). Spindle shaped centro-acinar cells are prominent in atrophing acini; moderate fibrosis exists only around ducts and bloodvessels; fat is not conspicuous; an occasional large, well formed island; transitions of islands to acini.[1]

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[1] A detailed description and discussion of the relation of islands to parenchyma is here omitted as having no bearing on this issue. See later

3.   A13–16.   Female, age 54.   Death in diabetic coma. Duration of disease 8 years.   Pancreas 15 cm. long.   Weight 120 grm.   Head relatively broad, measures 8 cm. across; its centre and tail only 2 cm.   Head occupies about 5 cm. of whole pancreatic length; the rest is only represented by a narrow strip. Section shows wide separation of lobes; no fat infiltration, no sclerosis.   Microscopically: *advanced severe atrophy of paren-chyma with general collapse of lobar architecture.*   The lobules are very small and show an almost complete collapse of acinar arrangement   Small polygonal cells, irregular in size, often not larger than large lymphocytes, with smooth, well staining protoplasm and a small central or excentric deeply staining nucleus, occupy diffusely the lobular spaces.   They are held together and separated by an extremely thin fibrillar reticulum. (Fig. 2.)   The main lobular arrangement has, therefore, become completely disorganized, only peripheral parts of some lobules still allow recognition of acinar remains and, in some lobules, preserved, but very small acini.   Even their lining cells are much changed and resemble closely those of collapsed parts: they are small, cuboid, polyhedral or round, possess a smooth, well staining protoplasm and deeply staining nuclei. They are increased in number and sometimes the lining is formed by a multi-nuclear syncytium.   Typical glandular cells are not to be seen anywhere.   Occasionally a narrow slit-like lumen is still visible in these acinar remains; often even this is no longer to be seen.   A limited fibrosis exists around the otherwise well preserved ducts and bloodvessels, and fibrils radiate from these spots in very thin and limited bands into surrounding parenchyma.   They are soon lost or termin-ate in few places in small, irregular hyaline patches.   There exists no general or essential fibrosis, and fat is present only in scanty drops in the lobules and in moderate amount between them.   Islands or their remains are absent.

We are dealing in these cases with a lesion which differs essentially from those so far described and proclaimed as characteristic of diabetes. Its feature is atrophy of parenchyma leading to collapse of pancreatic structure and disorganization of glandular architecture, but it is not a cirrhotic loss, or productive fibrous pancreatitis. The atrophy is associated with rather active formation of new cells which, however, are correspondingly undeveloped and irregular in type.

It would appear that these three cases, together with the case observed several years ago, are genetically related: the first represents the least advanced. In it the pancreatic make-up is still generally preserved, although evidences of beginning structural collapse are evident. This is more pronounced in the second case. In it the formation of new cells becomes conspicuous, while the third, together with the case previously observed, is most advanced in these features and shows profound alterations.

What, then, is the nature of this atrophy and disorganisation, in absence of any evidences of inflammatory changes, fat replacement of circulatory disturbances?

In this respect certain observations of Reitmann on the evolution of the normal pancreas appear of interest. The occurrence of degenerative and regenerative pictures in the adult pancreas of healthy and non-diabetic individuals have led him to the conclusion that the pancreas is physiologically an unstable organ which undergoes continual regression and progression. These lead gradually to a complete change and reconstruction of the organ, and this is accomplished by a physiological correlation between retrogressive and progressive changes, which ensure the integrity of the gland. Reconstruction may even go so far as to lead to the formation of new lobules, which are gradually introduced between older ones. These observations of Reitmann acquire great interest in regard to the cases of pancreatic atrophy associated with severe diabetes recorded above, for, if it is true that the pancreas undergoes constant physiological degeneration and regeneration, then it may be supposed that these cases represent

only pathological exaggerations, and that this atrophy, with the occurrence of the numerous atypical new cells replacing old collapsed parenchyma, is an expression of cell exhaustion coupled with, necessarily aborted regenerative attempts.

The importance of this matter from the general point of organ life and in its special relation to diabetes prompted a further investigation of this subject which was, therefore, undertaken by Dr. C. M. Anderson of this laboratory and the writer, the results of which are presented in the subsequent paper. But, whatever may be the explanation, it is certain that an essential atrophy of pancreas leading to loss of, and disorganisation of remaining, pancreatic parenchyma associated with abortive, atypical regenerative attempts, is characteristic of a type of severe diabetes.

Finally, with regard to the fate of the islands of Langerhans in these cases. They take part in the general atrophy and collapse of pancreatic parenchyma, but only with, and apparently following, that of the parenchyma. Independent structural changes were not observed in them, but it becomes increasingly more difficult, as parenchyma wastes, to differentiate islands from the surrounding atrophying portions. Few islands may remain intact until late (Case 2), and these appear large and prominent within the surrounding atrophic tissue.

The largest number, however, seem to collapse with the rest of the organ, thus making it impossible to identify and differentiate them with certainty; or pictures appear which are evidently transitions from islands to acini. The evidence of these cases does not, therefore, support the view that the islands play an essential and independent rôle in diabetes, but rather that these structures are inter-related parts of pancreatic parenchyma.

This finding is in harmony with the experimental results of Milne and Peters, who demonstrated not only the intimate relation between islands and parenchyma in experimental pancreatic atrophy, but also emphasized the difficulty of differentiating morphologically remaining groups of parenchyma

cells, especially when surrounded by connective tissue, from islands of Langerhans, a fact which has undoubtedly often misled investigators.

Important in this regard is, further, that hyaline changes in islands identical with those in diabetes have been observed in non-diabetics, especially seniles and cachectics. Milne and Peters mention this, and Reitmann, who also draws attention to the fact, does not hesitate to regard island changes in diabetes as secondary, due to cachexia or superadded infections (tuberculosis with hyaline or amyloid degenerations), conditions to which diabetics are extremely liable.

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EXPLANATION OF PLATES

Fig. 1. Case 2. Death in diabetic coma. Irregular general atrophy of pancreatic parenchyma. Acini collapsed, poorly outlined, acinar cells very atrophic. In parts, increased nuclei (occasionally syncytial) irregularity in size and shape of acini with some hypertrophic.

Fig. 2. Case 3. Death in diabetic coma. Complete collapse of pancreatic architecture. Aborted regeneration by small, diffusely arranged, polygonal cells. Few large fat drops.

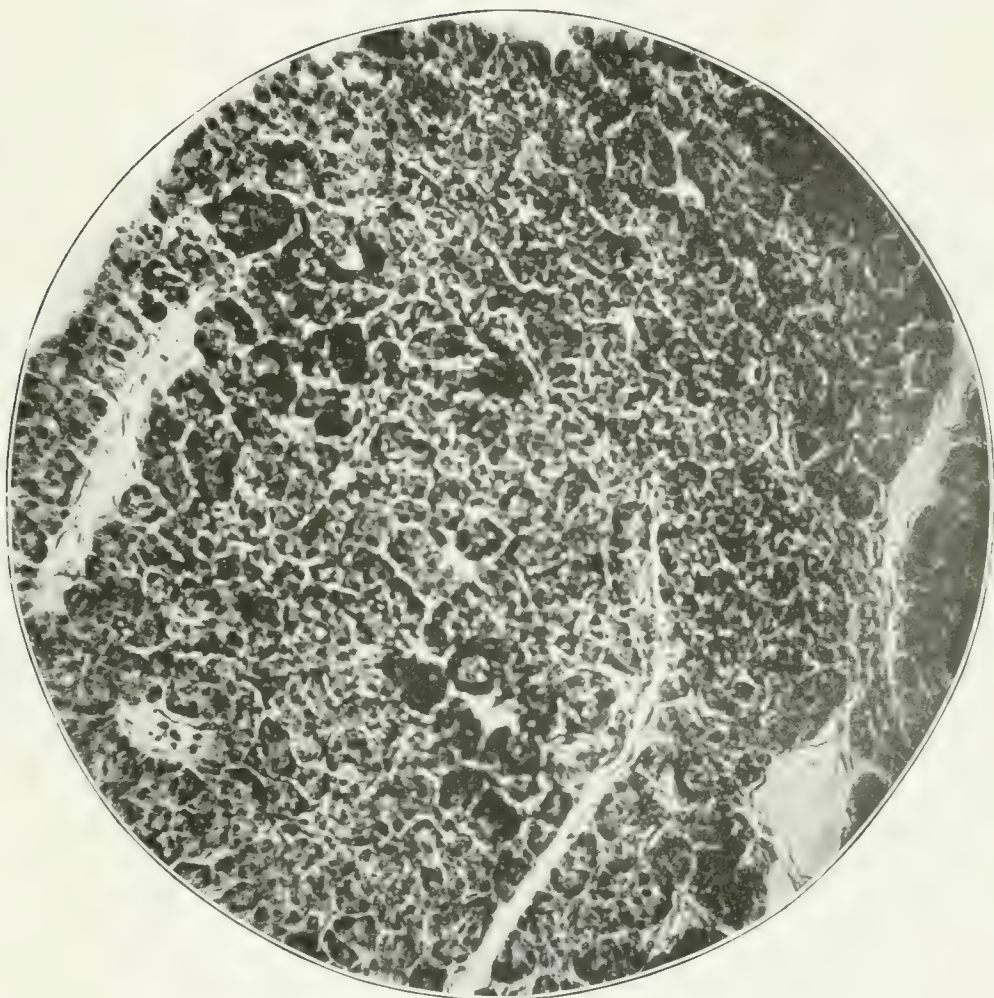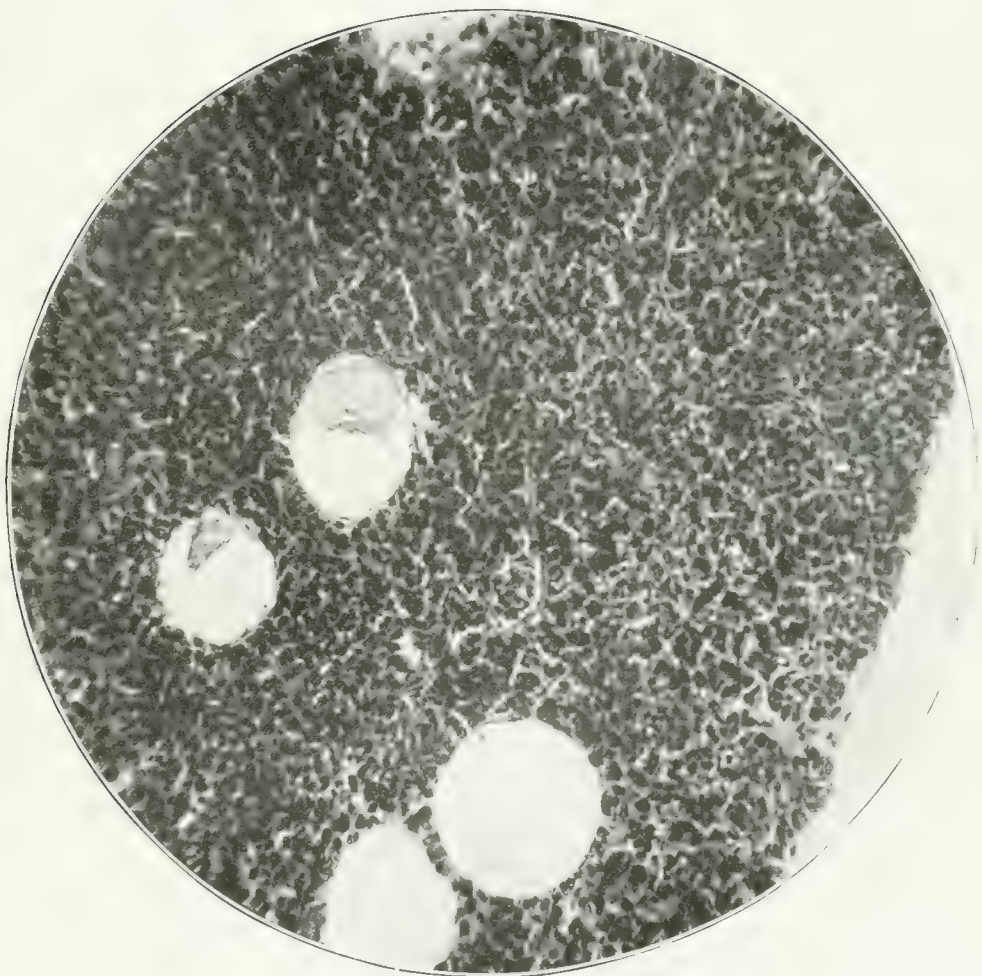Note absence of cirrhosis and fat replacement in both cases.

Fig. 1

Fig. 2

II

REGRESSIVE AND PROGRESSIVE CHANGES IN THE PANCREAS

A CONTRIBUTION TO POST-NATAL ORGAN EVOLUTION IN ITS RELATION TO DISEASE

By Horst Oertel and Charles M. Anderson

Anyone who examines the pancreas microscopically, as a matter of routine, will soon be struck by the frequency with which variations from normal structure as well as cell types are encountered in cases in which neither clinical history nor gross anatomical changes at time of necropsy point to any lesion of the organ   These changes may be limited and localized, but occasionally assume dimensions extensive enough to appear pathological and quite sufficient to be brought into connection with severe pancreatic functional disturbances, but for the fact that evidence of these has been lacking before death.

The changes referred to affect the parenchyma exclusively; they are not, as will be explained more fully later, inflammatory, but essentially atrophic or degenerative loss of parenchyma leading to diminution in size of acini, even tubular collapse, and associated with more or less extensive formation of new cells which may differentiate themselves into new acini. Thus appear characteristic, but unusual, cell types and tubular structures and arrangements.   The character and significance of these changes acquired growing interest in the study of several cases of fatal diabetes observed in this laboratory during the last year and reported by one of us.   These showed alterations so closely resembling changes in the non-diabetic cases that they appeared fundamentally identical, possibly only exaggerations of the variations in the non-diabetic cases.

Interest was further stimulated by an article of Reitmann (*Zeitschrift f. Heilkunde Abt. f. path. Anat.*, xxvi, 1905, p. 1. ff),

who detected pictures in the normal pancreas similar to some
observed by us and who interpreted them not as pathological,
but as physiological regressive and progressive evolutionary
stages.

His observations and conclusions are, shortly, as follows:
In the normal pancreas occur first, groups of acini which show
marked deviations from the normal in enlarged, extremely
well outlined cells which possess (in H and E sections) a plasma
staining uniformly red and very delicately granular. The
normal intercellular secretory capillaries to the tubular lumen
have disappeared. The nuclei of these cells are pushed toward
the base, are often pyknotic, i.e., markedly shrunken—show,
therefore, a variety of shapes and are homogeneous in their
staining qualities. In some of these cells the outline becomes
more accentuated by a disappearance of cell plasma, and only
a honeycombed network remains. Thus they bear a resem-
blance to sebaceous epithelium. They are enlarged and their
intercellular secretory capillaries are necessarily markedly nar-
rowed. Other acini show only simple atrophy with intact cell
nuclei.

A further change consists in the appearance in tubules of
centrally located, homogeneous red, polygonal protoplasmic
masses with a convex border towards the lumen. In these
masses threads extend to the basement membrane. They are
not made up of definite cells and nuclei lie quite irregularly
within them, are of normal form, but have apparently lost their
chromatic scaffold.

Finally, in certain acini are seen isolated, swollen cells,
compressing their neighbours, with a bright distinct outline,
waxy protoplasm and a basal, often shrunken, nucleus.
Secretory capillaries between these cells are absent.

Reitmann rejects the idea that these various pictures
represent secretory phenomena, for the reason that they are
too strictly localized and show a great variability in form.
But common to all is a severe destructive change in the cell
plasma with regressive changes in the nuclei. They must,
therefore, be degenerative in nature.

These changes may be found in every normal pancreas past middle life and certainly cannot be regarded as pathological. Furthermore, associated are compensatory regenerative phenomena. These are exhibited by somewhat enlarged acini whose lining cells are still lower than normal, typical, cells, but contain a normal nucleus. They possess a plasma corresponding only to the outer zone of a normal functionating cell and of fibrillar structure. An inner zone and ability of zymogen production are lacking, as well as secretory capillaries between the cells. The lumen of such acini is filled by small, polygonal, homogeneous red cells with oval, chromatin-poor, often shrunken nuclei. These cells are gradually eliminated and a lumen established. Thus all kinds of transitional pictures to normal gland tubules may be seen.

Reitmann concludes from these findings that the pancreas is physiologically in constant regression and progression, leading to a complete change and reconstruction of its elements, and that a physiological relation exists between both processes which ensures the integrity of the gland. The reconstruction goes so far as to lead to the formation of new lobules which are gradually introduced between the older. This phase of the process seems to be most active in early life, for the weight of the pancreas increases from about 4 grm. in the third month after birth to about 100 grm. in the adult, an increase which cannot be explained by simple enlargement of cells.

In support of his contentions Reitmann points to observations of other, earlier, investigations. Thus, Nussbaum found similar, localized, cellular and nuclear changes and isolated, dislocated cell groups. Kühne and Lea have also observed groups of polyhedral, strictly circumscribed, closely packed cells with little protoplasmic substance and large nuclei. They interpreted these, however, as pathological formations. Similar findings were made by Lewaschew and Kölliker-Ebner, and finally, numerous, especially modern, investigations have emphasized the presence of cell groups which seem to represent transitions between islands of Langerhans and acinar tissue.

We have, for purpose of this publication, recorded the findings in the pancreas of 22, with exception of one, consecutive autopsies, all of these in non-diabetics, in which death had occurred from various, widely different, acute and chronic lesions. The general results may be tabulated as follows:

Totally unchanged...................... 3
With quantitative changes only (irregularity in size of acini and lobules)..... 2
                                        ——
                                         5

Showing definite qualitative alterations: 17.

These were distributed through various age-periods as follows:

1 to 10 years...................... 3
10 to 20 years...................... 1
20 to 30 years...................... 2
30 to 40 years...................... 1
40 to 50 years...................... 2
50 to 60 years...................... 5
Over 60 years...................... 3
                                    ——
                                    17

The qualititative changes met with in these may be classified and summarized as follows:

1.   Degenerative and atrophic changes:

These are easily recognized in isolated cells or the whole lining of an acinus, even several or groups of acini. In hæmatoxylin eosin preparations these cells stand out distinctly by virtue of their homogeneous, pale reddish, smooth swollen protoplasm, which at once differentiates them from normal neighbouring cells. Even when several, or groups of, acini are involved, not all cells of an individual acinus may thus be affected, and many show a gradual change from normal granular cells to the swollen homogeneous type. This homogeneous protoplasm undergoes further change, becomes paler, fades, and ultimately the cell body disappears; the cell outlines which at first are rather accentuated become

indistinct and the part collapses. Nuclei of these cells undergo later a corresponding atrophy, shrink, fade, and disappear by chromatolysis, and two or more nuclei may be seen in such cells. Fig. 1. Sometimes hyaline masses fill the lumina of acini thus affected. These cell changes and disarrangements produce occasionally pictures somewhat resembling islands of Langerhans, but can be differentiated by their intimate connection with acini and the presence of less advanced changes in acinar cells at the periphery of these groups. Increase in nuclei in, and at the periphery of, these disintegrating areas is frequent.[1]

These pictures are irregularly, but occasionally very generally, distributed through the pancreatic parenchyma, sometimes being abundant in a lobule, entirely absent in others, or found only after considerable search. The most pronounced change of this type, and one which formed the basis of this description, occurred in our series in the pancreas of a woman of 24 years with a marked mitral (funnel shaped) stenosis (fibrous, healed endocarditis), who died suddenly after a premature labour. A. 27'16. The pancreas at time of autopsy (6 hrs. p.m.) was described as of normal size, firmer than usual and of pale-purple-gray colour. Nothing in the patient's history had pointed to any pancreatic lesion.

Similar changes were also conspicuous in a male of 58 years who died of lobar pneumonia with fibrinous pleurisy: pancreas without gross lesions A. 1'16 (8 hrs. p.m.); and in a male of 66 years who died of thrombosis of the left iliac artery and its branches (gangrene of legs) and general arteriosclerosis, pancreas small and firm A. 30'16.

With the exception of this last case, in which existed moderate arterio-sclerosis and localized sclerosis in the pancreas, other pathological nutritive or inflammatory lesions of the pancreas were entirely absent in these cases, and evidences of post-mortem autolysis were lacking.

[1] It will be seen that these changes are essentially different from post-mortem cell autolysis in character and distribution.

Similar, but less extensive pictures were seen in the pancreas of a number of other cases. These degenerative lesions may occur in combination with simple cell and acinar atrophy, but the latter may also, as already mentioned, appear alone and lead to a considerable, although generally irregular, collapse of acini.

2. Cell and tubular formation in pancreatic parenchyma:

Regeneration or regenerative attemps in parenchyma cells are, as appears to us from our experience, extremely frequently met with in pancreas, unsuspected of pathological lesions, and intimately connected with the foregoing degenerative and atrophic conditions. This combination was well illustrated in the pancreas of a female, age 48 years, who died from a sarcoma of the left tibia with metastases in lung and liver; A. 12'16. Grossly the pancreas had shown no abnormality, but microscopically cellular degeneration, acinar atrophy and collapse were evident in a great variety of pictures and very diffuse. In addition to these changes described above, existed frequent dilatation of acini, sometimes with tubular distortion, the lumina filled with desquamated cells or cell remains or hyaline pale material. Often the lining of these dilated acini was represented by low, smooth, multinuclear syncytium; in others the lumen was filled by new small cells; collapsed acini showed also evidences of active cell formation, and even in preserved acini nuclear increase (16 and more) within small, rather indefinitely outlined cells, occasionally obliterating the lumen, could be noted. In this instance, as in some others, the newly formed cells were generally small, more or less undifferentiated and did not assume a specific character in shape, collection to independent aggregates and in tinctorial qualities. These distinguishing features, however, occurred in other cases.

In these we could distinguish between two types: the first, in which irregular groups of not fully differentiated evidently germinative cells appeared, more or less diffusely, between acini or in collapsed parts; the second, in which definitely localized collections of similar cells, of characteristic

tinctorial qualities and arrangement, were interpolated between, and connected with, the parenchyma.

First, then, the appearance of apparently germinative cell groups within acinar parenchyma. These were seen in the pancreas of a male of 65 years, dead from chronic productive nephritis with heart hypertrophy and hydrothorax: pancreas small and firm—A. 5'16; a male of 51 years who died of an endothelioma of the pleura with metastases in heart and lungs: pancreas small and firm—A. 180'15; a male of 73 years, dead from an ulcer of stomach: pancreas without gross lesions—A. 49'16; and occurred especially diffuse and pronounced in a male of 52 years, dead from chronic gout, nephritis and myocardial degeneration, but without clinical evidences of diabetes—A. 18'16. Pancreas showed no gross lesions, but microscopically very marked alterations in size and shape of acini, many very small, atrophic, others hypertrophied with increase in nuclei and a much higher, almost cylindrical epithelium with smooth, uniformly red (h. and e.) protoplasm. Besides these changes, however, there were areas in which the acinar arrangement had been lost and taken up by round and polygonal, individually well outlined, often multinucleated cells, irregular in size, but generally smaller than the normal pancreatic epithelium. They possessed a smooth, pale red protoplasm and laid in close proximity. Such groups were in intimate contact with surrounding preserved acinar parts and occasionally merged in them. Fig. 2. These cell groups had all appearances of recent, proliferating, unarranged parenchyma cells. Degenerative changes were not seen in these sections. The pancreas showed no other anomalies, its ducts and vessels were intact, and islands of Langerhans were well defined and numerous.

The second type of new cell formation, in which more definitely localized and arranged, distinctly eosinophile, groups of cells connected with the acinar parenchyma appear, was well illustrated in a male of 40 years who died of tetanus—A. 43'16. This pancreas showed no gross lesions. Microscopically, very characteristic pictures were found: the lobules were

for the most part regular, well shaped, and the acini presented generally a normal appearance, only varying in size.

They were lined with typical, granular, well formed epithelial cells whose protoplasm stained deeply with basic dyes. Interpolated, however, were numerous, large, well defined groups of different sizes and shapes made up of closely packed cells, which at a glance stand out prominently from the rest of the darker, acinar parenchyma by virtue of their bright eosinophile, smooth, supple protoplasm containing one or several well staining small round nuclei and a round or polygonal, sometimes high, almost cylindrical shape. Fig. 3. They are in intimate contact with the acinar parenchyma, and while the central parts of these cell masses are devoid of any structural arrangement, their periphery exhibits not infrequently tendency to acinar formation, and some surrounding well formed acini show similar distinctly eosinophile cells. Where the tendency to acinar arrangement is manifest, cells become higher, adhere to each other, their protoplasm becomes polychrome as in the older parenchyma cells, and a small slit-like lumen appears.

These cells groups are easily distinguished and quite different from the flat, pale islands, of which a good typical number were seen. Otherwise the pancreas was intact, and its ducts and vessels essentially unchanged.

Lastly, there are cases (in our series from a few days after birth to twenty years of age) which cannot be regarded as regenerative changes within well developed parenchyma, but which seem to represent a very general organ development or reconstruction. In an infant of six days, male, dead of an imperforate anus (patent foramen ovale) A. 42'16, the pancreas (without evident gross abnormality) showed an as yet very undeveloped and incompletely differentiated parenchyma. Large cell masses with many vesicular nuclei were either still very diffusely collected, or formed incomplete, tortuous and irregular tubules. Even in parts where acinar arrangement had furthest advanced, increase of nuclei and lack of definite lumina indicated incomplete maturity. Ducts, however, were well formed.

A female of three weeks with congenital syphilis, A. 46'16, pancreas without gross lesions, showed much greater advance in development in good looking, well shaped acini and cells, in addition, however, many as yet undeveloped germinal groups interchanging with the others. Fibroplastic proliferation was also to be seen in and around the developing centres (Syphilis?). In a female of four months which had died of subacute cirrhosis of the liver and broncho-pneumonia, A. 19'16, pancreas without gross lesion, general acinar and cellular differentiation and numerous well defined islands, all structures in close contact, were found. Increase in nuclei within lining cells of acini was plainly visible. (Initiation of further growth?)

Finally, most interesting was the pancreas of a young male, 19 years old, who died of chronic endocarditis of the mitral valve (stenosis and insufficiency): A. 9'16, pancreas grossly with evidences of stasis only. Microscopically, the parenchyma showed very general and extensive changes. Almost all the acini are atrophic or collapsed, becoming thus widely separated. In other places, however, there occurs in addition marked increase of small, round deeply staining nuclei and small polypmorphous cells. Conspicuous within such areas are much larger, better developed, polygonal cells united either to masses, cords, or solid, tortuous, tubular columns. They possess a supple, deeply staining, occasionally multinucleated and syncytial protoplasm and, therefore, stand out prominently against the atrophic, small-celled, paler portion.

These solid cell columns are often surrounded and shade into large irregular, racemose acini still without a lumen. Such acini occasionally also surround and are connected with multinucleated islands of flat protoplasmic masses and cells. Fig. 4. Small, deep, eosinophile, polygonal cells (as described above) in isolated groups of few are also seen. The ducts are well formed and lined, and a moderate amount of fat is between the lobules, but does not infiltrate them.

A consideration of these findings shows a surprising fre-

quency with which changes from the normal are found in the pancreas, for, as seen by the tabulation of the 22 cases, only 3 were in all respects intact, while 2 showed at least noticeable quantative alterations in size of cells and acini. But omitting these, there still remain 17 in which often diffuse and marked qualitative alterations were discovered.

How can these findings be interpreted ? Have they, in the first place, a genetic relation to the diseases and causes of death in which they occurred ? We believe that this is most improbable, for reason of their uniformity, localization, absence of inflammatory or vascular lesions and finally their character, which is throughout only cellular loss and structural collapse and reconstruction in a manner closely related to embryonic and, as our own observations show, infantile gland development. It would, therefore, seem forced to us to regard these changes as results or dependent upon the various widely different diseases represented in this series. All that can be claimed in this respect is that these diseases may possibly indirectly enhance or exaggerate them.

Can we, in the second place, be dealing with direct results of normal pancreatic function ? We are inclined, with Reitmann, to deny that we have before us only evidences of secretory activity, for the reason that they consist not only of structural deviations within parenchyma cells, but loss of cells, acini and collapse of pancreatic structure together with cell proliferation, formation of new cells and acinar reconstruction. But while a direct connection with secretory cell activity seems. for these reasons, unlikely, a remote relation is possible, even probable, if we suppose that cell exhaustion, loss and regeneration are regular events in the life of this gland. This is indeed, in our opinion, the case, for it seems certain from the combined evidence of a number of isolated older investigations, Reitmann's and our own, that the pancreas is structurally an unstable organ. It shares in this respect the fate of other organs, notably of internal secretion, in our experience, for

example, thyroid, suprarenal gland and hypophysis cerebri.[1]

But the great extent to which these variations lead, in an organ regarded as healthy and grossly still within that range, is remarkably and unexpectedly attested by our series. Indeed, so great may these changes become that the microscopic examination of isolated parts might lead to a diagnosis of pancreatic disease where such has apparently not existed.

It is not easy to account for these manifold variations, unless we suppose that physiological individual differences exist, that in some exhaustion and loss of gland cells occur more readily and generally than in others, and that these are compensated by an equally active gland reconstruction which prevents the development to pathological states.

The intimate relation betweeen physiological and pathological processes is once more herewith exemplified, for loss of balance in one or the other direction initiates pathological lesions. That these may then be the foundation of severe functional derangements, such as diabetes, is made at least probable by the observations presented in the previous paper by one of us.

But this question may also be asked: are the changes in the pancreas alone responsible for the diabetic symptom complex, or are other additional, as yet poorly understood, factors required to complete the necessary links to a chain? How careful one must be in directly connecting anatomical organ changes with obscure functional derangements, especially when only parts of an organ are under observation, is well emphasized by the findings recorded above.

A new field is here still before us with ground for useful cultivation.

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[1] The investigations of Coplin on the Morphology of the Human Thymus (Publications from the Jefferson Med. College and Hospital, vi 1915, p. 116), point, it seems to us, in the same direction.
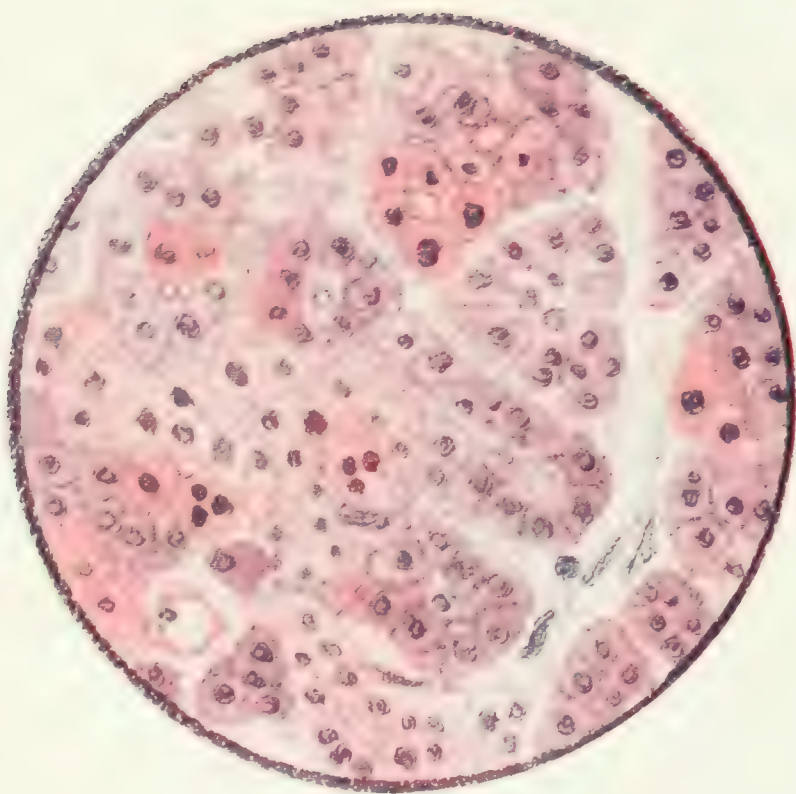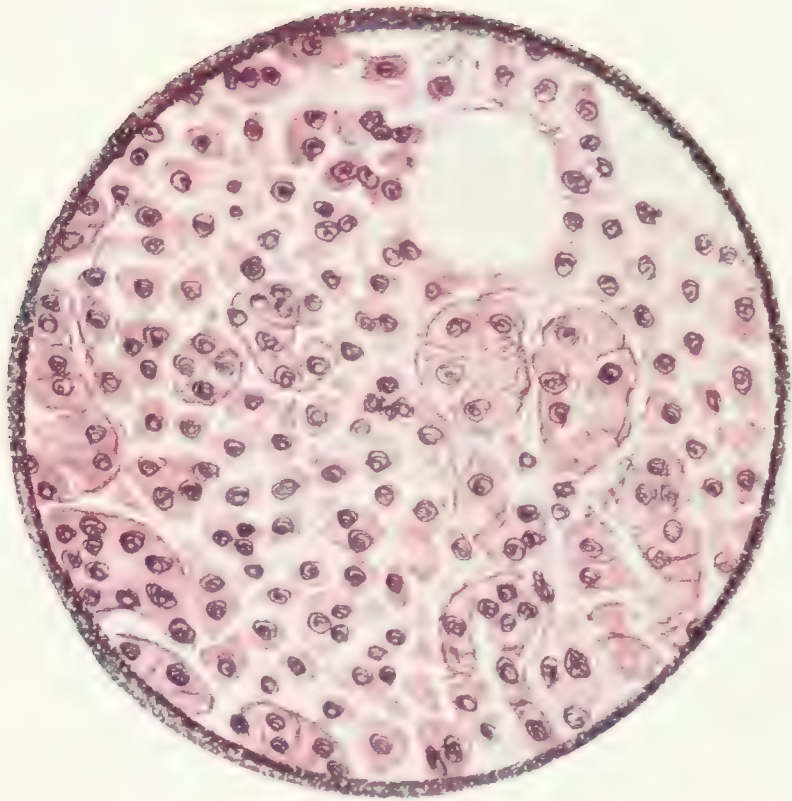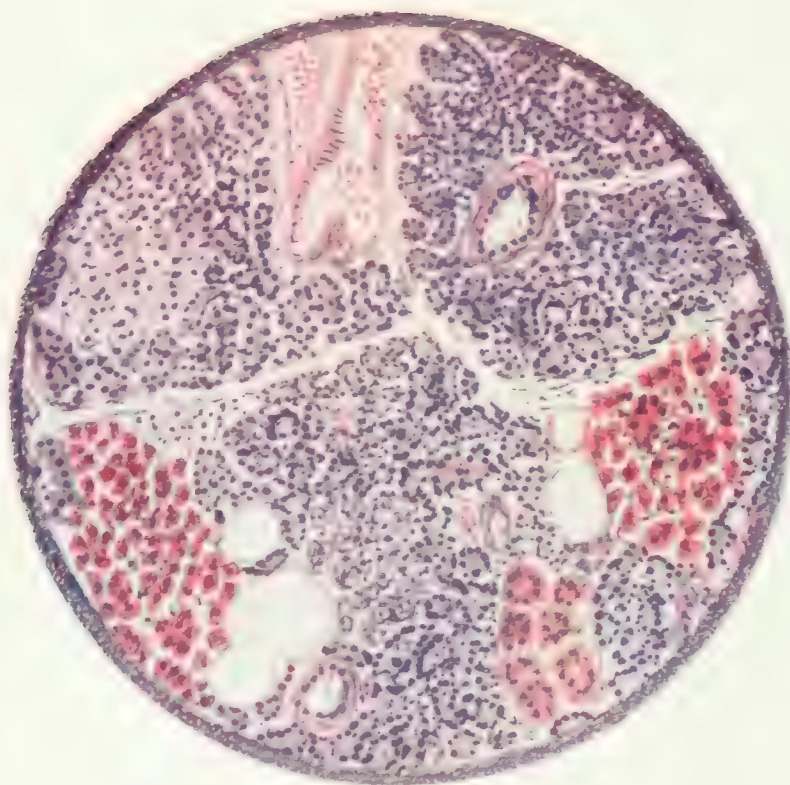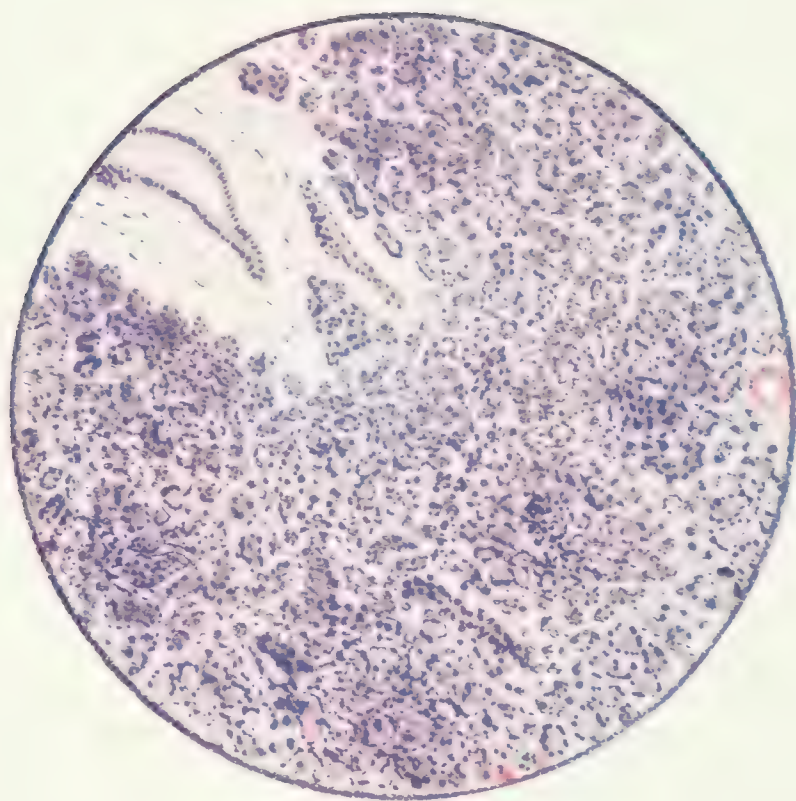
Fig. 1

Fig. 2

Fig. 3

Fig. 1

THE ORIGIN OF POLYPI OF THE GASTRO-INTESTINAL TRACT, WITH SPECIAL REFERENCE TO ACUTE INFLAMMATORY DISTURBANCE, AS ONE OF THE CAUSES

By Harry Goldblatt

(*From the pathological laboratories*)

A series of specimens of gastritis and colitis polyposa in the Medical Museum of McGill University, together with a case of acute dysentery[1] at the Royal Victoria Hospital in which, at autopsy, the intestinal tract from the lower part of the ileum to the anus was found studded with polypoid outgrowths, raised the interesting question of the origin of true polypoid conditions of the gastro-intestinal tract. I present here a careful investigation of the literature on the subject, and the findings of gross and in microscopical section in the Royal Victoria Hospital case and six of the cases from the McGill Museum. As a result of this investigation I shall discuss the various modes of origin of polypi of the gastrointestinal tract, in what I consider the order of their importance, and shall attempt to show how these views are supported by my study of the cases above mentioned, and by the literature on the subject.

A. Inflammation as a Cause of Polypi

1. *Acute* inflammatory processes of the mucosa and submucosa.

In a search through the literature on this subject one finds frequently hints from investigators and from compilers of general pathology of the probable origin of polypi in the intestinal tract from *chronic* inflammatory change; only few (not-

[1]H. W. S., case of Dr. Garrow, Ward G, R. V. H., Adm. Oct. 8th, 1915, Died Oct. 27th, 1916.

ably Kaufmann, Aschoff and Ziegler) mention this condition as resulting from healed acute necrotic inflammations. How probable and how important a cause this is, is well illustrated by the case of acute dysentery to which I referred at the commencement of this paper:

H. W. ⸰. was admitted to the Royal Victoria Hospital on October 8th, with symptoms pointing to a very acute inflammatory disturbance (dysentery) of the intestinal tract. The patient died on October 27th, and at autopsy (Professor Oertel) the findings in the affected part were as follows (A. 165'15): Down to the lower part of the ileum the gastrointestinal tract was normal. In the lower three feet of the ileum, however, the mucous membrane was very much swollen and deeply congested. Here and there, in the mucous membrane, were longitudinal and transverse areas of ulceration varying from 1 cm. to 5 cm. in length, and from a few millimeters to 1 cm. in breadth. Near the ileo-cæcal valve the ulcerations in the ileum were scanty. In the cæcum and in the colon the mucous membrane was much more swollen and injected, and in many places was even hæmorrhagic in character. Areas of ulceration were more abundant and deeper in this part of the gut. Several wide longitudinal bands of ulceration were present, and these were everywhere crossed by transverse ulcerations which coalesced in many places. The ulcers, in most cases, took the shape of deep troughs cut through the mucous membrane, although some were round or irregular in shape. The base in every instance seemed to consist of highly inflammed submucosa. Since the ulcerations were very numerous and involved the whole thickness of the mucosa, with also a part of the submucosa, this left a few large, and numerous small islands of inflamed mucosa sitting upon stalks of thickened submucosa, which thus presented the appearance of polypi. In the descending colon ulceration was most marked, the submucosa being everywhere laid bare as a raw granulating surface studded with large and small sessile and pedunculated growths. One area about six inches long, and extending completely round the gut, was almost completely

denuded of mucosa, only a few small patches remaining, and these were also raised so far above the surface that they appeared like true polypi. In the rectum a similar condition existed, but the polypi were not as numerous Here some of the growths seemed to consist only of undermined mucosa which remained attached at one point. In one part of the rectum, as also in the cæcum, the entire margin of an irregularly shaped ulcer was thrown up into polypoid forms. On the whole, as is fairly well shown in the photographs, the interior of this part of the alimentary tract presented a picture hardly to be differentiated in its gross appearance from a case of so-called true enteritis polyposa.

Microscopical section of the wall of the intestine and through one of these polypoid growths (See Fig. 1) shows that mucosa remains only on the surface of its head. From the surface between the glands of the mucosa columnar epithelium is absent, as it is in most specimens of the intestine, even in the absence of inflammation, due to post-mortem digestion. The glandular tissue is in a hyperplastic condition, and, in one of the sections, is seen to have forced its way through the muscularis mucosæ to become embedded in the submucosa. The mucous cells are very much increased in number (See Figs. 2 and 3) and are very full, showing signs of the hyperactivity which is a usual accompaniment of inflammation of the mucosa and which initiates cystic changes in the glands. The spaces between the glands are increased in size due to the accumulation of inflammatory cellular elements, so that the glands are abnormally separated from one another. The pedicle of the "polyp" (See Fig. 3) consists of densely infiltrated connective tissue continuous with that of the submucosa of the intestinal wall, and is, in fact, merely thickened submucosa on all sides of which deep ulceration has occurred. From the free surface of this pedicle, and from the intestinal wall for some diatance around the growth, the mucosa is entirely wanting, and the submucosa is exposed as an acutely inflamed, granulating surface. The stalk seems to consist almost entirely of cellular elements (see Fig. 3), so great is the

infiltration. Polymorphonuclear leucocytes, lymphocytes, and endothelial cells of various shapes and sizes, abound and almost obscure the matrix of connective tissue. The dilatation and vast increase in the number of capillary bloodvessels ramifying in this region, complete the picture of the active process of repair which was evidently going on in this region at the time of death of the patient. The submucosa of the wall of the intestine in the vicinity of the "polyp" presents the same appearance as that described for the stem of the growth So intense was the inflammation of the intestine in this case, that the connective tissue of the muscular wall, as well as the subperitoneal tissue, are also infiltrated with leucocytes, lymphocytes and endothelial cells (see Fig. 3).

What occurred in this case is quite evident. The mucosa and submucosa became acutely inflammed, the latter more than the former, with the result that the mucous membrane became markedly thickened. Ulceration then took place promiscuously throughout that part of the intestine, removing the whole depth of the mucosa and several layers of submucosal cells in very many places. Wherever mucosa remained, it rested on a stalk of thickened submucosa, and the two thus formed a growth which resembled a true polyp in the gross appearance. Numerous such growths dotting the wall of the gut presented a picture similar to that of true "polyposis intestinalis." Had the patient lived, and had repair continued as it seems to have been doing at the time of the patient's death, it seems reasonable to think that cicatrization would have occurred, and healthy mucosa grown over the denuded surface of the intestinal wall and pedicles of the growths from the numerous areas of mucosa that were still left. The heaped up islands of mucous membrane would then have remained, their growth continuing as a result of the irritative hyperplasia of the mucosa, thus leading to a typical polyposis of the intestinal tract which might have been discovered only as an accidental finding in a "post-mortem" years later. It is true that cases of the kind that I have described are rarely seen—in fact, I have failed to find an identical case reported—but that is probably due to

the fact that such particular varieties of dysentery rarely
come to autopsy during the acute stage, and when they do,
later on, the origin from acute inflammation is probably
obscured by later changes in the process of repair.   In addi-
tion, if a history of an acute inflammation of the bowels at one
time is not obtained, then the *acute* inflammatory origin of a
polypoid state of the intestines, discovered accidentally at
post-mortem, is sure to be overlooked.   Here, however, in the
case which I have described in detail above, we are particularly
fortunate in being allowed to look at the state of the intestinal
wall at the time when it was very acutely inflamed.   The
cause of the polypoidal state is therefore quite evident in this
case, and it seems reasonable to assume that, if the patient had
recovered, the bowel would have remained in the state usually
described as colitis or enteritis polyposa.   That such is also
one of the ways in which polypi originate in the stomach is
difficult to prove and is perhaps doubtful, because those who
have reported cases of gastritis polyposa have not given a
clinical history of *acute* inflammatory disturbance.   Yet, in
the light of the findings in the case described above, one must
admit that such an origin, even in the case of the stomach, is a
reasonable possibility

2.   *Chronic Inflammatory Processes of the Mucous Mem-
brane.*   The chronic inflammatory changes leading to the pro-
duction of polypi in the gastro-intestinal tract are probably of
two kinds.   One form is characterized by general inflammation
of the mucous membrane, especially of the submucosa, with
ulceration, and the other is the slow, long continued, hyper-
plastic type of inflammation.   The first type is beautifully
demonstrated in a case of chronic entero-colitis described by
Woodward, 1881, in which the gross autopsy findings were not
unlike that of the case described above, although apparently
a more chronic condition.   Many areas of ulceration were
still present in the intestinal mucous membrane, but micro-
scopically it was found that cicatricial contraction had oc-
curred around the heaped up islets of mucous membrane
which had remained between the ulcerations.   Chronic irrita-

tion of the mucous membrane on these growths had caused it the hypertrophy, and parts of it to become scytic. With the sole exception that mucosa was still absent from the surface of part of the pedicle and from the intestinal wall around the latter, the section of a polyp which he described differed in no measure from some of the sections in my series taken from cases of true gastritis and colitis polyposa. Yet Woodward described his case as one of "pseudo-polypi," and did not suggest or think that true polypi would have resulted had the patient lived. Another case of chronic diarrhœa, observed by Menzel in 1720, in which the autopsy findings were similar to those of Woodward's case, was cited by Virchow as a case of true colitis polyposa. But Woodward considers it another illustration of pseudo-polyposis. If he means by the word "pseudo" an early stage in the process of formation of the so-called "*true*" condition, then I agree with him, for I believe that the case he has described, and the case which I have described, are both examples of the early stage of true colitis polyposa, resulting in the former form chronic, and in the latter form acute, inflammation with ulceration of the mucous membrane. When ulceration occurs, there is a likelihood that if polypi result they will be rather numerous, and I am inclined to believe that this occurred in one of my cases. Microscopic section of one of the polypi in this case shows all the signs of chronic inflammation which I shall describe in the next paragraph; but no signs of past ulceration are discoverable, as the mucous membrane is intact, and there are no definite signs of cicatrization. The gross appearance, however, does not differ much from that of the acute case. In this case the beautiful specimen of colitis polyposa was, as in many cases, an accidental finding. The patient, aged 64, was admitted to hospital with Huntington's Chorea. A very incomplete personal history was obtained from the patient, who died not long after admission. Since there were evidently no symptoms present at the time to direct the house surgeon's attention to the bowel, he failed to obtain a history of any disturbance in that region at any time previous. This might have helped materially to

establish the exact origin of these polypi. I have no proof
to offer that ulceration is an accompaniment of chronic inflam-
mation as a cause of polypi in the stomach, and I have not
been able to discover any reference to this in the literature.

The other form of chronic inflammatory change, the hyper-
plastic type, which causes the formation of polypi, and is per-
haps the principal way in which they originate in the stomach,
is well illustrated by some of the cases from the museum. With
the exception of one case, all the specimens of polyposis present
signs of chronic inflammation. In two of the cases the mucous
membrane of the stomach wall seemed thickened, and in the
other two distinctly atrophic. The latter condition is evidence
of a late stage of chronic inflammation. The sections of
gastric polypi all present signs of the existence of chronic
inflammation. They all show the presence of a thickened
mucosa, the result of inflammatory hyperphasia, in the glands
of which cystic changes have taken place—"common enough,"
as Woodward says, "in chronic catarrhal conditions of the
mucosa." The submucosa in every case, especially in the
region of the polyp, is markedly thickened and follows right up
into the polyp, thus constituting the main bulk of its pedicle.
Throughout these polypi small-celled infiltration is compara-
tively abundant and the blood supply is very plentiful. All
these are unmistakable signs of chronic inflammation.
Although I have suggested that the case of colitis polyposa
probably originated from inflammation accompanied by ulcer-
ation, yet in microscopical section it presents a similar appear-
ance to that of the ones just described. In this case the extra-
ordinary increase in the number of bloodvessels, some of large
size with thickened walls, and others which are merely dilated
capillaries, is very remarkable. Some of the other sections
also show very thickwalled vessels, and this is perhaps caused
by the increased force with which blood must be driven through
a narrow contracted pedicle. The obstruction to the outflow
of blood from the polyp by the narrow pedicle may account
for the dilated venules and capillaries. The presence of

chronic inflammation explains, of course, the presence of many of the dilated capillaries which ramify in this region.

The sequence of events in the cases described above seems to have been the following: Chronic inflammation of the wall of the organ occurred, causing thickening of the mucosa and especially of the submucosa, and giving to the mucous membrane the appearance called the *état mameolonné*. In some places, especially near the pyloric end of the stomach, the submucous hypertrophy was very marked, and thus excrescences were formed which were covered with a layer of inflamed mucosa thickened on account of chronic irritation. These excrescences were true polypi. The rest of the mucous membrane of the organ either continued to be chronically inflamed, or became atrophic. Unfortunately, in this case, as in most of the others which I obtained from the museum, a clinical history was absent; and this is to be deplored, since it might well have told a story of chronic inflammatory disturbance in this organ.

Many observers, without attempting to prove it by reference to definite cases, have recognized that chronic inflammation of such a nature is probably a cause of polypi of the gastro-intestinal tract. W. Collier reported a case of multiple polypi of the stomach and small bowel in which, for a period of one year before death, there was a history of pain across the abdomen, vomiting, and diarrhœa with bloody stools. Post-mortem, an enormous number of polypi, varying in size from that of a pea to that of a pigeon's egg, many with long pedicles, were found throughout the stomach and intestine. He did not give a microscopical report nor even a detailed account of the gross findings, so that it is difficult to say whether ulceration was an accompaniment; but it is certainly safe to assume from the history that chronic inflammation was the cause of the condition.

Adami, in discussing a case of intestinal polyposis of Dr. Lapthorne Smith, before the Med. Chi. Society of Montreal, exhibited a case of ulcerative colitis with numerous papillary growths, from the McGill Pathological Museum, and pointed

out the frequent relationship which such growths bear to chronic inflammatory disturbances. He also stated there that "the increased nutrition in the hyperæmic zone around old ulcers, for example, might originate such overgrowth of the mucous membrane in these positions as to cause the formation of 'adenomatous polypi.'" Adami, however, mentioned the fact that not all cases of polypi gave a history during life of inflammatory disturbance of the gastro-intestinal tract.

Carl Wegele, in a description of a case of multiple polyposis of the stomach, favours the view of their origin from chronic catarrh of the organ. And *Riegel* refers to the probable formation of polypi from chronic inflammation of the gastric mucosa, through the *état mameolonné*, followed later by atrophy of the mucous membrane except where marked thickening of the submucosa had taken place. "In such places," he says, "the mucosa becomes heaped up and, increasing in thickness due to irritative hyperplasia, finally forms a true polyp."

Lebert describes the presence of a very large number of polypi in the colon of a patient who had suffered for a long while from a bloody diarrhœa. In this case, however, inflammation must have been excessive, and an abundance of granulation tissue changed the polypi into fibrous tags.

Luschka reported a case of prolonged dysentery with bloody stools in which, at autopsy, sessile and pedunculated polypi were present in thousands from the ileo-cæcal valve to the anus. "The polypi themselves consisted of tubular glands resembling the glands of Lieberkuhn, except that they were longer and many branched and held together by a partly fibrillated and partly granular connective tissue in which naked nuclei and nucleated cells were embedded and numerous blood-vessels ramified. The mucous membrane between the polypi was not markedly altered." This is not unlike the picture which some of my sections present. From the description which I have given of some of my sections, and from the extracts which I have quoted, it is therefore quite plain that chronic inflammation plays a very important role in initiating the production of polypi.

B.   ADENOMATOUS HYPERPLASIA OF THE MUCOSA AS A CAUSE OF POLYPI

As a primary cause of polypi, adenomatous overgrowth plays an important part both in the stomach and in the intestinal tract, and this is most evident when the condition occurs in infants and children.

One of the cases of gastritis polyposa in my series is clearly an illustration of such overgrowth. There is a very marked increase in the amount of typical glandular tissue to a thickness at least five times that of the rest of the gastric mucosa, which is apparently of normal depth. Neither the muscularis mucosæ nor the submucosa follow up into the polyp, but rather act as a horizontal base upon which the growth rests. The submucosa and muscularis are both very thin in this region. Although the specimen is rather old, the sections stained well and show that small-celled infiltration and signs of past inflammation with cicatrization are definitely *absent* in this case. The nuclei of the normally-shaped glandular cells also stain well and there seems to be very little increased vascularization. The cystic condition to be observed in some parts of the section are most probably due to obstruction of lymphatics from some cause, or to some degenerative change which often occurs in any adenomatous growth. We have here, therefore, an illustration of a polyp originating from an adenomatous hyperplasia of the mucosa.

Nothnagel states that such polypi occur very frequently in children, and Dr. Oertel suggests that the condition for that reason is probably due to the "particular architecture of the wall of the viscus in its embryonic condition," which leaves, here and there, heaped up areas of mucosa that take on adenomatous change and form polypi. Dr. Adami refers to such an origin as "blastomatoid"—and this is analogous to Konig's "congenital anlage." Smoler accepts Konig's congenital anlage idea, but assumes that a "pathological hyperæmia" is required to initiate the overgrowth. A probable illustration

of the last statement is the description by Thos. Smith of three cases of multiple polypi of the lower bowel which occurred in one family. This would seem to point to the congenital anlage idea; and the fact that the polypi developed to the extent that they could be diagnosed clinically only at the ages of 16, 18 and 20 years, probably signifies that the "pathological hyperæmia" did not occur until that late date.

The irritative hyperplasia, often termed adenomatosis, which occurs in the mucosa of those polypi that have evidently originated from inflammatory change, is a very important secondary cause of such growths, and accounts in a great measure for the large size which some of them attain. This form of glandular overgrowth is undoubtedly closely related to primary adenomatous change—but in such cases it does not constitute the process which initiates the formation of the polyp. Great overgrowth of glandular tissue might obscure the inflammatory origin in some cases, and that probably accounts for the predominance in the literature of cases of polypi called primary papillary adenomata. Inflammation, of course, as some investigators claim, may be the initial cause of all adenomata; but, until we know more about the origin of tumours in general, we must differentiate those polypi which are seemingly spontaneous and those which are closely related to inflammatory change. And that is why I mention adenomatous change as a primary cause of polypi.

C. Cystic Change in the Mucosa as a Cause of Polypi

In discussing inflammation and adenomatous overgrowth as primary causes of polypi, I have already mentioned the frequency with which cystic change may be observed in both conditions as a secondary manifestation. That this condition often sets in rather early is very beautifully demonstrated in the acute inflammatory case of Dr. Oertel, which I described in detail above (see Figs. 1 and 2). As a primary cause of polypoid formation it has been described by R. Virchow in a case he termed "colitis cystica polyposa," and Woodward

refers to this by saying: "This is the ultimate result of a process, which, in a lower degree, is common enough in chronic catarrhs of the colon—namely, the invasion of the closed follicles by the adjoining glands of Lieberkuhn, the terminal branches of which dilate into cysts." Woodward himself has reported several cases in which the cystic tumours found projected into the lumen of the intestine as little hemispherical tumours one-tenth to one quarter of an inch in diameter. In a case reported by J. Cruveilhier, "many of the cysts were pedunculated," so that the case was intermediate in degree between the most advanced of the cases reported by Woodward and the one reported by Virchow, in whose specimen the morbid process had progressed to a greater degree. Although most writers are agreed that inflammation is, as a rule, the cause of cystic change, yet, when inflammatory hyperplasia and small-celled infiltration are not present as an accompaniment, then in such cases, as in Virchow's cases, one must consider the cystic condition as the primary cause of the polyp. However, in the cases of gastritis and colitis polyposa from the museum, the sections show that cystic change is present only in *parts* of the growth, the main bulk of the polyp consisting of thickened submucosa and mucosa, so that there the cystic condition is apparently a secondary change. This can be considered a cause of the polyp formation only inasmuch as it accounts for part of their size.

D.   Vascular Changes as a Cause of Polypi

The vast number of bloodvessels that are to be seen in some of the sections, suggested to me the possibility that an increase locally in the number of bloodvessels, or dilatation of those present, due to some cause other than inflammation, might initiate the formation of polypi. This would be a sort of angioma in the submucosa which would lift up the mucosa, and, causing it to project into the lumen of the gut, where it would be subject to chronic irritation, would end by forming a polyp. While such a condition is conceivable, yet I have

failed to find a description of such a case in the literature, and none of the cases I have investigated illustrate this perfectly. The nearest thing to such a condition is present in the specimen of colitis polyposa which I have mentioned before. A section of this shows the presence of an enormous number of blood-vessels. Only the larger thick-walled vessels show in the photographs, but under the high-power lens the tissue is seen to be riddled with larger and smaller bloodvessels and capillaries to a remarkable degree Fig. 5, which is a photograph of somewhat higher power than Fig. 4, shows the irregularly dilated capillaries. None of the other sections show such a marked vascularization, and if it were not for the fact that there is definite thickening of the submucosa with small-celled infiltration, and that this polyp is only one of very many in a case of colitis polyposa (see Fig. 6), one would be inclined, from the microscopic examination alone, to consider this as an illustration of local dilatation and proliferation of bloodvessels initiating the formation of a polyp.

E.   DILATATION OF LYMPHATICS AS A CAUSE OF POLYPI

Owing to the age of the specimens which I have studied, definite knowledge of the state of the lymphatics is difficult to obtain. What are apparently lymphatic dilatations in the sections may be due merely to a shrinking of the tissues in some places. But Cripps is reported to have described a case in which he considered that varicosity of the lymphatics due to some obstruction had initiated the formation of the polypi. I have no proof to offer on this point by reference to the cases I have studied, but merely mention this since I consider dilatation of lymphatics as an important secondary change in all polypi—probably accounting in some measure for cystic conditions—and because Cripps' case suggests the probability that it may be the mode of origin of polypi.

SUMMARY

I have attempted, in this paper, to indicate the various ways in which polypi of the gastro-intestinal tract may originate.

These conclusions may, I believe, be drawn as to the causes of polypi in the probable order of their importance:

A. Inflammatory changes of the mucous membrane, acute or chronic, and with or without accompanying ulceration.

B. Primary adenomatous hyperplasia of the mucosa.

C. Cystic change in the mucous membrane.

D. Vascular changes.

E. Lymphatic changes.

While I have indicated that every cause mentioned may act separately in initiating the condition, yet it is evident that several of them usually act in combination.

Finally, I wish to express my sincerest thanks to Prof. Oertel, Dr. Maude E. Abbott, Dr. Kaufmann and Dr. Scott, for providing me with the material for this research and for valuable suggestions how to study the material.

The photographs were made by Mr. W. Muir, of the Anatomical Department of McGill University.

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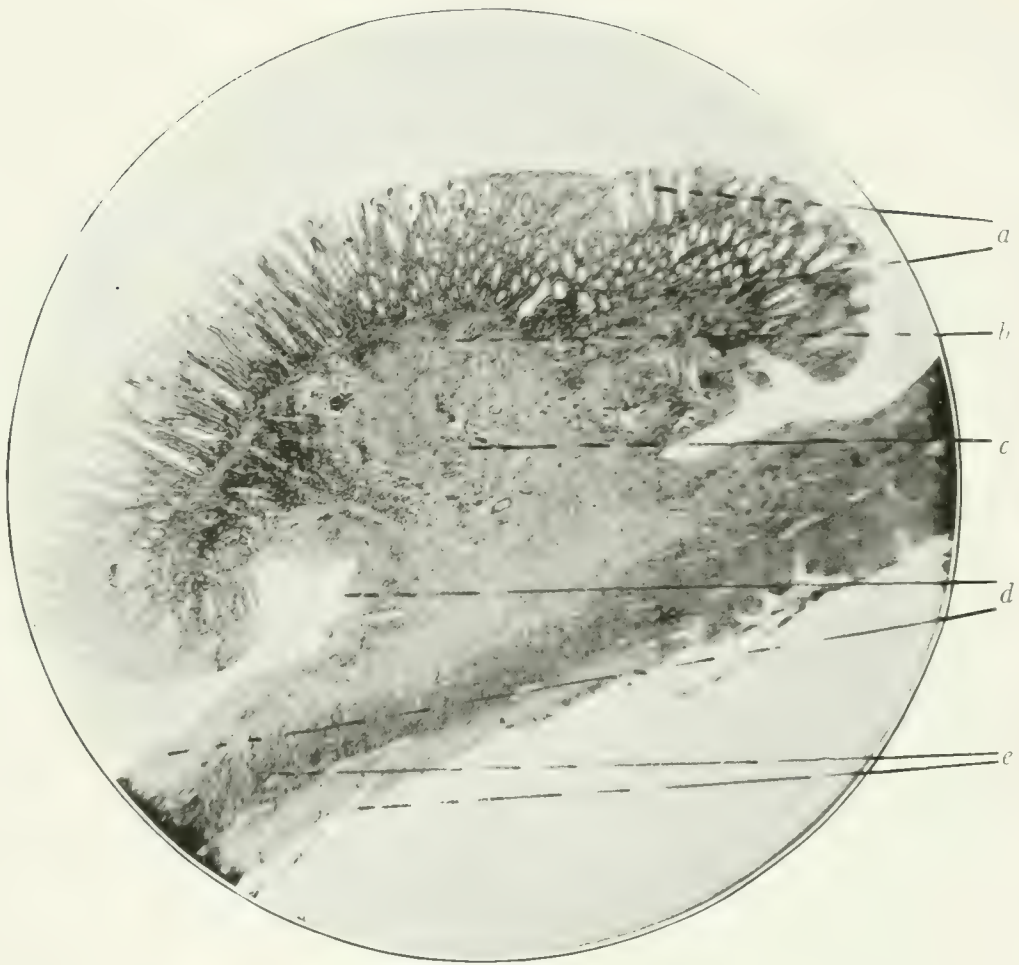WOODWARD, *Am. Journ. of Med. Sci.*, lxxxi, 1881, Art. xiii, p. 142.

Fig. 1.—Section through a "Polypoid Growth" of Colon. Low Power. × about 75. *a* Densely infiltrated, injected, and cystic Mucosa. *b* Muscularis mucosæ. *c* Pedicle of the "Polyp". *d* Mucosa ulcerated away. *e* Inflamed muscularis and subperitonial tissue.
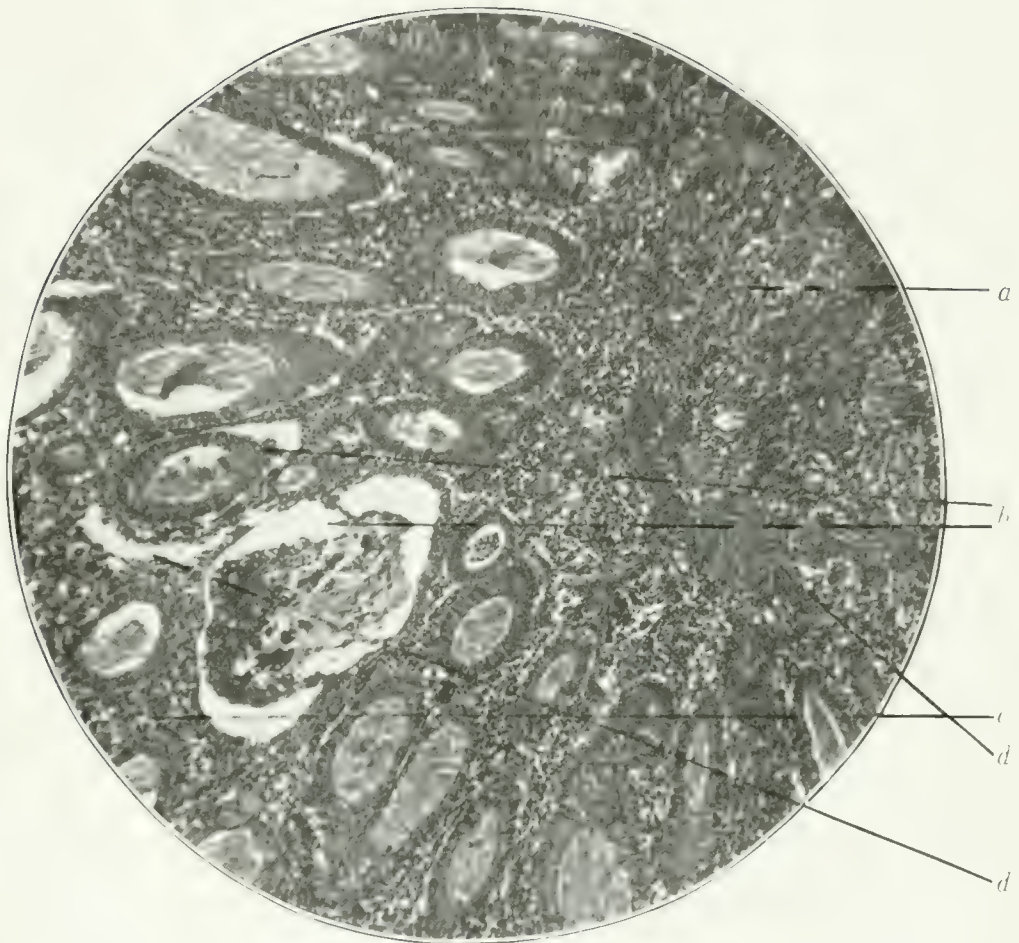
FIG. 2.—SECTION SHOWN IN FIG. 3, UNDER HIGHER POWER × 150. PART OF THE MUCOSA AND OF THE STEM OF THE POLYP ARE HERE SHOWN. SEE SLIDE IA. *a* Pedicle densely infiltrated with inflammatory cell elements. *b* Cystic glands of Mucosa. *c* Small celled infiltration between the glands of Lieberkühn. *d* Dilated Capillaries.
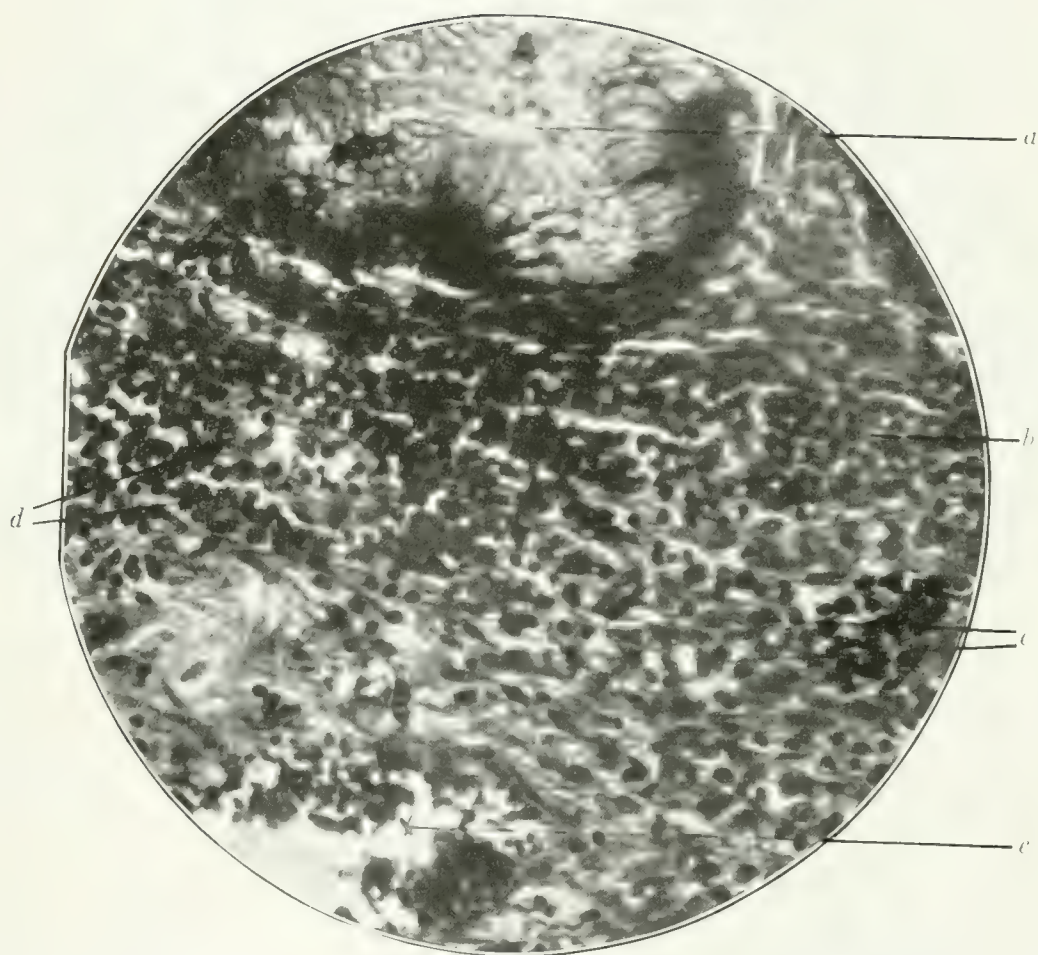
FIG. 3.—High power photograph of part of Mucosa and of Pedicle of the "Polyp" shown in Fig. 1. × about 400. See Slide Ia. *a* Cystic gland of the Mucosa showing proliferation of goblet cells. *b* Lymphocytes. *c* Leukocytes. *d* Endothelial cell. *e* Dilated Capillary.
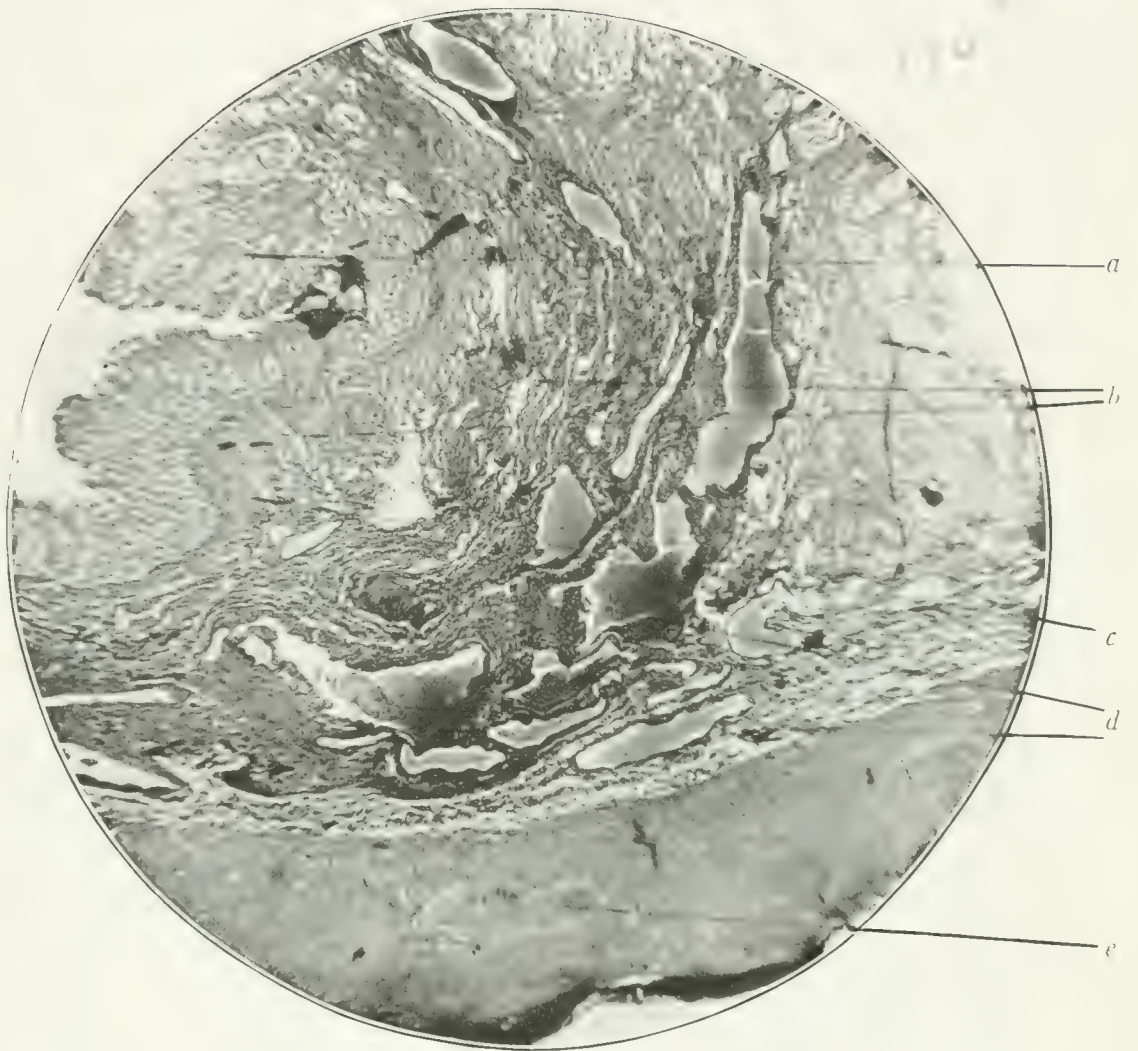
Fig. 4.—Section through part of a polyp from specimen shown in Fig. 6. See Slide II. × about 75. *a* Infiltrated and cystic Mucosa—somewhat thickened. *b* Muscularis Mucosæ and core of submucosal connective tissue passing up into the polyp. *c* Small cell infiltration of submucosa. *d* Enormously dilated blood vessels with thick walls. *e* Muscularis does not take part in the formation of the polyp.
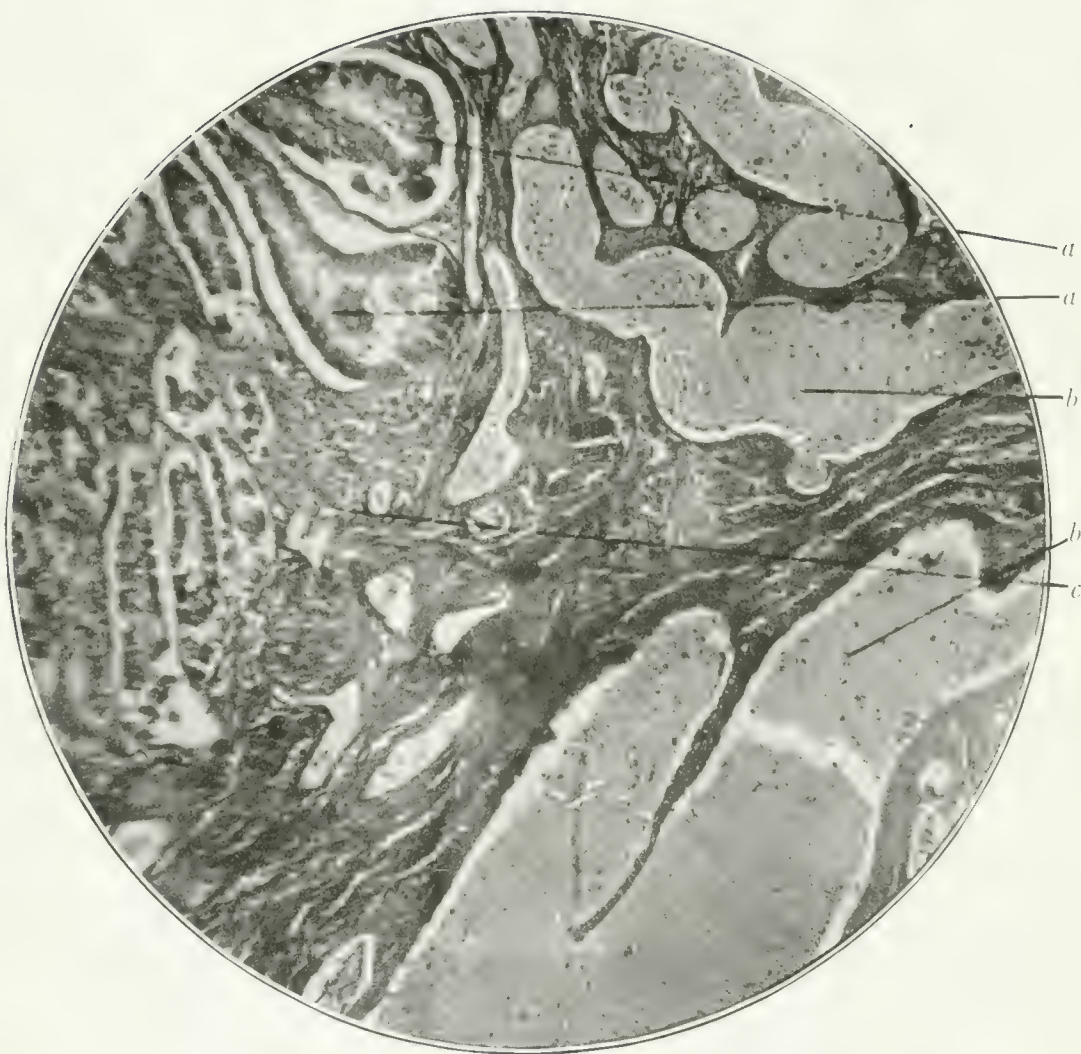
FIG. 5.—HIGHER POWER MAGNIFICATION OF SECTION SHOWN IN FIG. 4. SEE SLIDE II. × ABOUT 150. *a* Cystic glands. *b* Irregularly dilated blood vessels. *c* Lymphocytes.
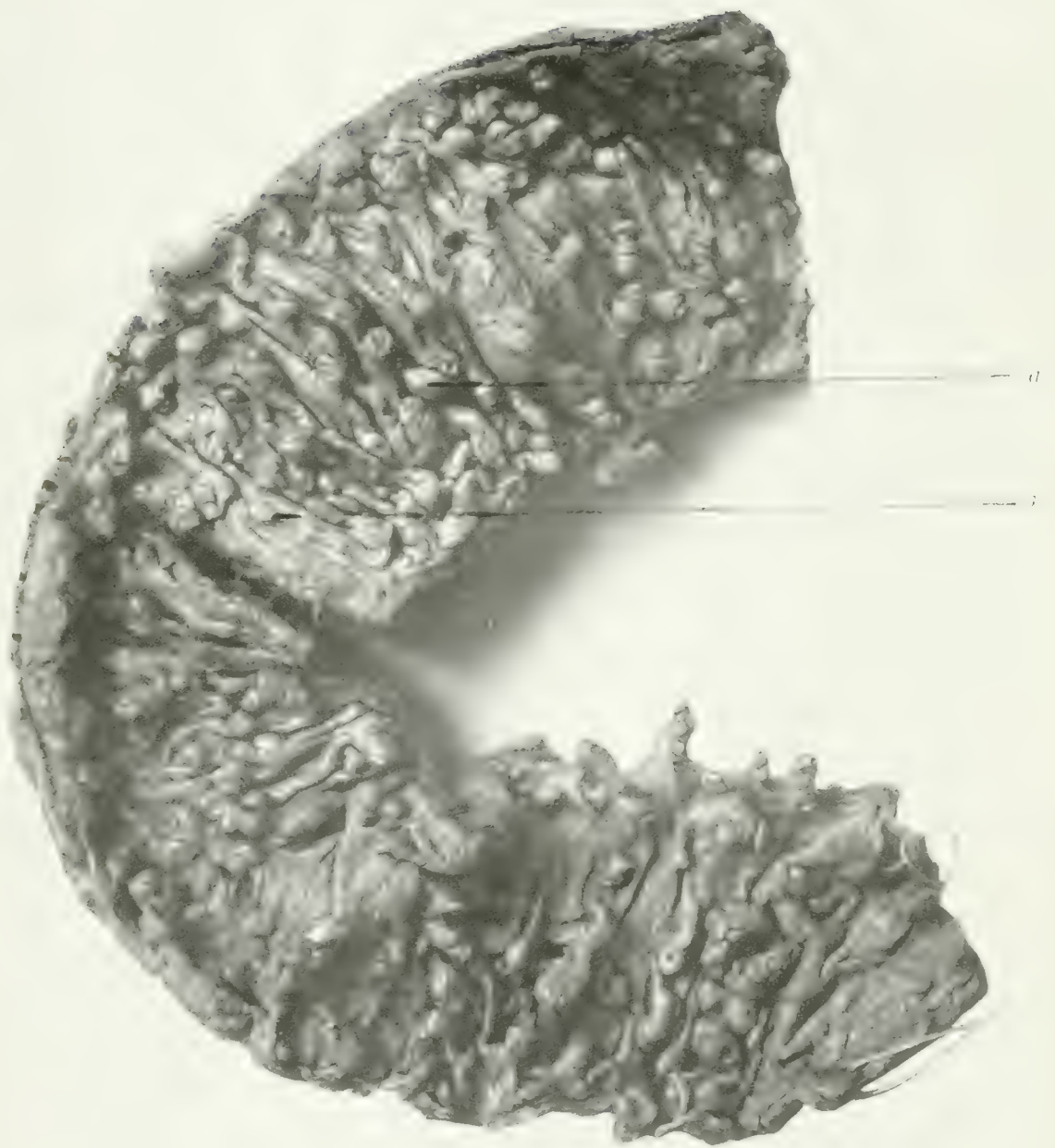
Fig. 6.—Part of Colon from a case of Colitis Polyposa, McGill Pathological Museum. *a.* Polypi riding on folds of mucous membrane. *b.* Polypi between folds of mucous membrane.

AN UNUSUAL (PROBABLY SYPHILITIC) SPLENOMEGALY

By Horst Oertel

(*From the pathological laboratories*)

This spleen was an accidental finding in the necropsy of a man who died, shortly after admission to the Royal Victoria Hospital, as result of an injury. Consequently there is no complete history or record of physical and blood examinations. The only information received at time of post-mortem examination was that patient was struck on the perineum and scrotum by an iron bar while at work, which immediately was followed by great pain and swelling of the parts. The following day he was admitted to hospital. The findings then were: male, white, Canadian, 42 years, fairly well nourished, with markedly swollen scrotum, size of a grape fruit, deep purple in colour. Right groin also swollen and discoloured as far as the anterior superior spine of the ileum. Of his previous history it was only known that he had pleurisy on the right side three years ago. His condition continued a fairly good one until the sixth day after admission, when evidences of infection were found which were relieved by multiple incisions in the right groin and scrotum, and drains inserted. During the following night he had considerable hæmorrhage from these and developed rapidly the symptoms of a general septicæmia. He died during the evening of the seventh day after admission.

At autopsy, A. 39–15, the tissues of the scrotum were found œdematous and gangrenous, and the adjoining perineum equally so. There existed also hæmatoma of the abdominal wall extending from the pubis to about 2 cm. below the umbilicus. No ascites. Heart with concentric hypertrophy of the left ventricle. The right pleura showed adhesions between the lobes, but was clean over the surface. On the surface of

the lower lobe of the left lung were a few minute tubercles, and near the base was a larger calcified, slightly contracted superficial area, but the apex was free. Granular, moderately contracted kidneys. A very unusual condition, however, was found with regard to the spleen. This occupied almost completely the left hypochondrium and was adherent by dense fibrous adhesions to all the surrounding organs and structures. Above, it was bound firmly to the diaphragm; on the side, to the stomach and tail of pancreas; and below, to the kidney and suprarenal gland. On removal it proved to be very markedly enlarged. Weight 1225 grm., measurement 12 x 12 x 9 cm. The surface showed deep scar contractions, dividing it into irregular lobes and giving the organ somewhat the appearance of the lobated liver in syphilitic cirrhosis, while its surface, although covered by shaggy thickened capsule, was not irregular, granular or nodular. Vessels at hilus intact. The organ as a whole was firm and, on section, it offered resistance, leaving a smooth cut surface which presents a very characteristic mottled appearance, due to diffuse irregular markings on a pale greyish ground substance from which the normal splenic tissue elements have completely disappeared. These markings consist of reddish streaks, dots and blotches. In addition there occur, particularly at the periphery, fibrous scars. These correspond to the previously mentioned interlobar depressions and extend into the spleen as irregular, coarse trabeculæ. They traverse the splenic substance in the form of whitish hyaline bands which occasionally show yellowish discoloration, and surround, and follow the course of, bloodvessels, so that their walls are continuous with thick scar tissue. Where these vessels have been cut in longitudinal or oblique section, they may be followed in the form of threads or short bands. Occasionally such bloodvessels occur within the hæmorrhagic blotches and streaks (see appended drawing).

Microscopic examination from various parts of the spleen show loss of pulp and lymphoid tissue throughout, with replacement by a diffuse fibrous growth which has very generally obliterated the normal structure. The fibrous tissue increase

occurs in two forms: around and in the neighbourhood of blood-vessels in the form of thick, poorly nourished, hyaline, fused, homogeneous connective tissue bands (corresponding to gross appearance). These carry not infrequently yellow to greenish blood pigment and show occasionally slight calcification. They follow the course of bloodvessels and are distinctly outlined from the surrounding cellular tissue. In this the normal structure of the spleen has given way to various pictures: first, areas in which the tissue is made up of a diffuse arrangement of polymorphous cells—small and large lympho-cytes, polyplasts, plasma cells, a few large flat (pulp or endo-thelial ?) cells, pigmented phagocytes, and fibroplasts.* All these posses deeply staining nuclei and are occasionally multi-nuclear. They appear loosely embedded in an irregular fibrillar reticulum. Such areas are generally avascular, only long, embryonic, endothelial buds exhibit attempts at capillary formation. These parts display, therefore, in a measure, the character of granulation tissue. Surrounding them are much dilated and engorged preserved venous sinuses. Secondly, areas in which a diffuse growth of long fibroplasts predominates and in which other cells have greatly diminished. These areas are, therefore, less cellular, and fibroplasts have matured to long, fibrillar, wavy form, but are rather unhealthy in appearance, although never actually necrotic. Thirdly, fields with atrophy of lymphoid corpuscles and pulp, in which, how-ever, the normal structural arrangement with sinusoids is still noticeable. But the walls of these sinusoids exhibit fibrous cellular thickening, and there is a diffuse appearance of fine, long, slender spindle cells. Finally, areas of irregular, marked blood stasis (hæmorrhages, infractions) in which free and fading red blood cells, blood pigment and a few disintegrating leuco-cytes and pulp cells make up the picture (correspond to gross hæmorrhagic blotches and streaks).

The foregoing description shows that we are dealing in

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* In spelling fibroplasts instead of fibroblasts, I follow a suggestion of Marchand (*Verhandl. d. deutsch. path. Gesellschaft*, 1909) who derives the word from πλάσσω, to form, and not from βλαστάνω, to germinate.

this case with a very exceptional granulomatous, productive, fibrous splenitis, leading to marked splenomegaly which exhibits a characteristic tendency to the formation of thick, hyaline retracting scars in intimate connection with bloodvessels. It differs, therefore, quite decidedly from the usual splenomegalies, only in parts it bears some resemblance to Banti's disease, but differs so much from it in essentials that it cannot be properly regarded as an example of that disease.

The etiology, in absence of evidence of exposure to tropical diseases, would seem to rest between tuberculosis and syphilis, and of these two syphilis seems, on account of the anatomical peculiarities, the most likely, although search for spirochætes was in vain. But it must be remembered that the process was advanced and the perivascular connective tissue hyaline and often degenerated, which would make the finding of possible spirochætes most difficult or even impossible. Other definite anatomical evidences of syphilis were, however, missing in the body. The liver showed only venous stasis and fatty changes.

If the supposition of a syphilitic origin of the lesion is correct, to which, in my opinion, the available evidence points, this splenomegaly forms one of the rare syphilitic diseases for reason of its general involvement of the organ, its late occurrence and lack of syphilitic manifestations elsewhere. Kaufmann, for example, who is well informed, states (*Lehrbuch d. spec. Pathol. Anat.*, vol. i, 1911, p. 148) that an appreciable splenic tumour without amyloidosis or lobated liver (absent in this case) almost never occurs in the tertiary stage of syphilis. Even gummata are rare. The lesion is, quite apart from its etiology, anatomically very exceptional in my experience.

TWO CASES OF RARE TUMOUR GROWTHS (ANGIO-ENDOTHELIOMATA), SHOWING UNUSUAL METASTASES

By C. T. Crowdy

(From the pathological laboratories)

During the last year two tumours, probably of angio-endotheliomatous origin, came to autopsy in the pathological laboratories of the Royal Victoria Hospital which were of exceptional clinical and anatomical interest on account of the seat of the primary growth and the very unusual metastases.

Case 1. A male, 52 years of age, admitted to the R.V.H. September 16, 1915, in the service of Dr. Hamilton, came to autopsy on October 17, 1915. On admission his complaint was pain in both legs, most marked in the right. The pain began three months previous in the region of the right knee. Up to that time he had enjoyed good health. Later the left knee became involved. The pain was paroxysmal in character, with sudden onset, lasting from a few minutes to half an hour, and was apparently behind the knee and not in the joint. A few weeks after this he had severe attacks of shooting pains down both thighs He was then admitted to another hospital for two weeks and improved, but when he returned home he was placed in a wet blanket and since then the attacks of pain have become more severe, in fact almost unbearable. On admission to the R.V.H. there were areas along the course of the sciatic nerve which were exquisitively tender. Urination was difficult and had to be aided by pressure over the abdomen. The patient has been in bed for the last two months. `

Personal History: Heavy drinker up to one year ago. Seven attacks of gonorrhœa in early life. No signs for past twenty years. Soft sores at age of 25. Denies syphilis.

Condition on Admission: Patient lies in dorsal decubitus; cannot assume any other position. His legs are wasted and he cannot move them easily. The inguinal glands are palpable, the abdomen full and moves freely with respiration. Liver just palpable beneath the costal margin. No tenderness.

Special Report by the Neurologist: Patient is very neurotic. Pupils small, sluggish, left more active to light than the right. Sensory: pain along course of sciatics. Right greater than the left. No sensory loss. Sphincters: difficulty in passing all urine. Involuntary defæcation.

Wasserman: Negative.

Skiagram: Showed indefinite outlines in sacral region.

AUTOPSY (ABBREVIATED) A. 158–15.

On opening the abdomen, no free fluid, liver 6 cm. below ensiform. Examination of the bony pelvis showed extensive necrosis of the promontory of the sacrum and partial destruction of both iliac bones by a soft hæmorrhagic growth. Liver 2050 grm. On the anterior surface immediately to the left of the round ligament there is a globular, slightly elevated, well circumscribed tumour mass measuring 6 cm. in diameter. It presents a mottled yellowish purple appearance, and the surface shows small congested vessels. On section the tumour is found to be about the size of a billiard ball and at first glance closely resembles a hæmatoma, but on closer examination fibrous tissue bands and numerous larger bloodvessels can be distinctly differentiated. Towards the centre the tumour becomes soft. Scattered throughout the liver are many similar nodules varying in size from a pea to a marble, which on section present the same appearance as the large tumour described above. The spleen near its centre contains a similar nodule, size of a large pea, otherwise without abnormality.

Careful examination of the prostate, adrenals and thyroid revealed no evidence of growth.

Microscopical Examination

The large globular, apparently primary, tumour is outlined by a zone of connective tissue. The tumour mass is made up of small, flat, round, oval and polygonal cells with a generally central round nucleus, rich in chromatin, surrounded by a zone of smooth, supple, acidophile protoplasm and a number of large giant cells with irregular, often convoluted, thick nuclei, closely resembling giant cells of bone marrow. In parts the cells are diffuse in their arrangement, sarcomatous; in others, however, a more characteristic make-up appears. The cells are joined, sometimes sitting on a delicate basement membrane in a way to form channels, columns or large alveoli. Characteristic is further the extreme vascularity of the tumour (corresponding to its gross appearance). The blood is partly diffuse, intercellular; in the structurally differentiated areas it is collected in large spaces or channels, the walls of which are formed by tumour cells and whose lumen also contains similar cells intermixed with blood cells. Thus there is established in parts a very intimate connection between tumour cells and blood, and in them a greater polymorphism of cells appears leading to pictures strongly suggestive of transformation of tumour into blood cells in close similarity to embryonic extra- and intra-vascular blood formation.* The smaller nodules in the liver and spleen, the growth in the sacrum and microscopic nodules later found in the kidney, were made up of similar cells and construction, but in the smallest, apparently most recent, foci none of the blood formation conspicuous in older nodules was to be seen.

The general appearance of the tumour resembles, therefore, a sarcoma; however, the arrangement of cells into channels and columns, the definite relation of these to surrounding cells and to blood formation indicate an endotheliomatous or

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* This autochthonous blood formation in human tumours has been observed and described by Albrecht, Borst, Hansemann, B. Fischer, Löhlein, Schmieden, and by Schmincke in an angio-endothelioma of a dog's liver.

peritheliomatous derivation of the growth, and the diagnosis of perithelioma of the liver with metastases in the liver, spleen, kidney and sacrum was made.

This tumour is noteworthy as a rare type of growth of the liver.

While cavernous capillary ectasies (so-called angiomata) are not uncommon in the liver as developmental anomalies, true angio-endotheliomata which depend upon distinct endothelial budding and formation of new bloodvessels in tumour like fashion occur with much greater infrequency. Such a case has been described in multiple form by Veeder and Austin in a child of ten weeks, and they also review the literature on the subject. Even much rarer are the malignant diffuse and infiltrating hæmangio-endotheliomata. Very few of these are recorded in the literature by Fischer, Löhlein and Nazari.

Unique in this case are, as far as I have been able to determine, not only the extensive, almost diffuse, metastases in the liver and other organs, but especially the involvement of the sacrum.

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Case 2. A male, age 28, was admitted to the R.V.H. November 5, 1915, in an unconscious condition, and died November 7th. He had been ill and absent from work for about two weeks, but not confined to bed. On November 3rd he was able to visit a physician, but became unconscious about noon November 4th. No further history obtained.

Physical Examination: A fairly well developed and moderately well nourished male. Face slightly cyanosed, pupils dilated and fixed. The left is slightly irregular. Respiration is increased in rate and expiration prolonged. From time to time the patient coughed up a thick, but not tenacious, slightly brown stained, mucus. The limbs are quite flaccid. The patient is in a comatose condition, cannot be aroused, and does not respond to any stimuli. The posterior cervical, inguinal and femoral glands are palpable. The chest fairly well developed. The costal margins flaring. Both sides move equally on respiration.

No dullness at the apices or bases. Moderate hyper-resonance throughout. Coarse rales over both lungs. Expiration is slightly prolonged. No bronchial breathing. Radials slightly thickened, but not tortuous; pulse equal in both, volume small. Tension 102. Rate 70. Rhythm irregular. Heart sounds clear; no murmurs Abdomen slightly scaphoid; no visible peristalsis. Bladder above pubis (?). The liver extends 7 cm. below the ensiform cartilage. On palpation it is firm, slightly rough, and the edge quite sharp. Spleen and kidneys not palpable. The extremities are quite flaccid; the muscles fairly well developed and firm.

The following reflexes present: biceps, triceps, supinator and patellar, double Babinski. Urine negative.

Spinal fluid clear, slightly yellowish; Nonne and Noguchi.+ Leucocytes 1.2 per cm., some red blood cells present.

Autopsy (Abbreviated). A. 171–15.

On removing the skull-cap some increase in the amount of fluid at the base of the brain was found. This fluid was slightly turbid. Externally the brain presented no gross lesions, but on opening the right lateral ventricle the floor was seen to bulge anteriorly into the ventricle and incision exposed a tumour occupying the position of the caudate nucleus, replacing its outer half, which easily shelled out, was globular, definitely encapsulated, measuring 5.5 cm. x 4 cm. Branches

of the middle meningeal artery ran into the tumour, which on section was found to be firm, dark in colour and very vascular.

No free fluid found in the pleural cavities. A few old apical adhesions present. A few c.c. of fluid in the pelvic cavity. Heart and vessels showed no gross lesions. The right lung weighed 900 grm.; pleural surface over the upper lobe is roughened by fibrinous tags. The upper lobe is bright red and on pressure exudes a dark frothy fluid. The left lung weighs 650 grm. Shows the same condition as the right, except that there is a nodule the size of a marble on the diaphragmatic surface of the lower lobe which on section is white and firm.

The left lobe of the liver contains a globular tumour about the size of an apple which can be plainly seen on both the superior and inferior surfaces. On section it is firm, shows a thin capsule, is white throughout its greater extent, with smaller yellow areas. Scattered throughout the liver are similar but smaller nodules. The right kidney contains one small nodule 5 mm. in diameter closely resembling those in the liver.

MICROSCOPICAL EXAMINATION

The sections from the brain tumour show a very characteristic picture. It is made up almost entirely of well formed bloodvessels and sinuses, filled with blood. The connecting and intervening tissue consists of flat polyhedral or elongated, uniformly medium-sized cells with an oval or round nucleus and a well marked zone of protoplasm. In places these cells are arranged at right angles to the long axis of the blood channels, and their direct connection with the lining endothium of these vessels can be followed. The growths in the lung, liver and kidney present on the whole the same features, except that open vascular channels are less numerous than in the primary growth, but the tumour grows in solid flat celled columns. Diagnosis: hæmangio-perithelioma of the brain with metastases in the liver, kidney and lung; chronic tuberculosis.

There does not seem much doubt that the primary tumour was in the brain; for this speaks the size, gross physical appearances of the brain tumour, as well as the microscopic findings, which in the liver and kidney were much more one-sided and less characteristic than in the brain. In the brain the growth consisted essentially of vascular channels separated by intervascular groups of endotheliomatous cells, while in the metastases the tumour grew almost entirely in form of solid cell columns.

Hæmangio-endotheliomata in the substance of the brain occur with greater infrequency than in the dura. Interesting in this case is further the circumscribed character of the growth, the absence of metastases in the brain itself, but occurrence of metastases in three distant and far apart organs

ANATOMIC CHANGES IN TRINITRO-TOLUENE POISONING WITH SPECIAL REFERENCE TO ITS NATURE

By Henry Odland

(From the pathological laboratories)

Patient, a male, age 20, medical student, went to work in a munitions factory about July 1, 1916, and remained there for about eight weeks, when he became jaundiced. During that time he was exposed to the vapours of trinitro-toluene, and was found on several occasions to have exposed himself voluntarily to the vapours of toluene.* The jaundice gradually increased in severity, but, after six weeks' treatment in the hospital of the factory, began to fade. Patient's general condition also improved, and he felt so well that he resumed in the autumn his studies in the Medical School. Suddenly, on October 18th, he began to have hæmorrhages from the nose and bowel and into the subcutaneous tissue. He became rapidly weaker, collapsed and died ten hours after admission to the Royal Victoria Hospital, and within forty-eight hours after onset of the bleeding.

Physical examination on admission to hospital revealed a well nourished, athletic young man, but prostrate. The conjunctival membranes showed faint icteroid tinge. On the anterior surface of the left thigh there were many small purpuric spots or ecchymoses. Axillary and inguinal glands palpable. The anterior nares blocked with blood clots. The examination of the lungs was negative except at both bases, behind where many medium-sized rales were heard at the end of inspiration. Accentuation of the apical heart sounds as well as of the pulmonary second. B.P. 110–60. W.B.C. 1,600.

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[1]The vapours of toluene seem, according to information of the physician at the factory, to possess intoxicating or exhilarating qualities.

The abdomen was rounded, and there was a slight diffuse tenderness over the epigastrium. Liver dullness extended from the sixth rib in the mid-clavicular line to 3 cm. above the costal border. There was practical anuria, and on catheterization 5 c.c. of bloody urine were obtained.

Autopsy 167–16.

External Examination: The body is that of a male 170 cm. long, and whose apparent age is 20 years. The physique and nutrition are very good. Rigor mortis is present, and there is post-mortem lividity of dependent parts. No definite jaundice. Over the thighs there are numerous subcutaneous hæmorrhages or ecchymoses, the largest 1 cm. in diameter. The pupils are equal and measure .5 cm., the teeth are in good condition, lips pale and gums white. The nostrils are filled with clotted blood. External genitalia show no gross lesions. The upper and lower limbs are very muscular and the chest is well formed.

Internal Examination: The lungs are voluminous and the anterior borders overlap. No fluid or adhesions in the pleura. The pericardium displays a dark hæmorrhagic area 5 cm. in diameter on the anterior parietal aspect; the liver is just visible below the costal margin and 5 cm. below the ensiform cartilage in the midline. The dome of the diaphragm is at the level of the fourth rib right and fourth space left. The omentum is thin and fatty, and hangs down in front of the moderately distended bowel. Beneath the serosa of the intestinal loops are numerous irregular, large ecchymoses. There are numerous adhesions easily broken down in the upper part of the abdomen between the various viscera, and a small amount of bloody serous fluid in both flanks.

Heart: Weighs 300 grm. The visceral pericardium shows small areas of ecchymoses. The pericardial cavity contains 10 c.c. of hæmorrhagic fluid. The apex is formed by the left ventricle. The tricuspid orifice admits two fingers, and the mitral two fingers. The valves are in good condition,

but there is some post-mortem hæmoglobin imbibition at the edges of leaflets. The heart muscle is pale in colour, and fairly firm, and also contains a few dark hæmorrhagic spots beneath the endocardium. The thickness of the wall of the right ventricle is .7 cm., and the left 1.5 cm. The aorta at its origin shows a few fatty plaques. The coronary arteries are free.

Right Lung: Weighs 510 grm. Is mottled pink in colour. The lung is voluminous and there is marked crepitation. On section it is bright red and congested and dry; the bronchi are clear. The left lung weighs 410 grm. and shows the same condition as the right.

Alimentary Tract: The mucosa of the stomach has a bluish appearance. The rugæ are fairly well preserved. Throughout the large and small intestine numerous small to large, hæmorrhagic infarctions or ecchymoses are seen beneath the mucosa.

Liver: Weighs 1760 grm. and measures 25 x 16.5 cm. The surface is generally smooth, bluish and the capsule not thickened, but there are definite, irregular, hæmorrhagic depressions which are partly streaky and partly patchy, and evidently correspond to collapsed areas. These are prominent over the right lobe. The left lobe is relatively small and smooth. On section the cut surface presents a very characteristic and unusual appearance. The whole left lobe is deeply reddened, flat and its vessels prominent. The liver tissue appears in it largely collapsed, and markings are obliterated. The whole right lobe is generally pale, gray, and shows tremendous parenchymatous swelling, which puts the lobular markings around depressed bloodvessels into a definite relief network. Parts of the right lobe show extension of hæmorrhagic, depressed collapsed areas from the left lobe into its raised, swollen parenchyma. The blood vessels of the right lobe are prominent, but bile ducts are not so, and the tissue is

not visibly jaundiced. The termination of the parenchymatous swelling in the right lobe is rather abrupt towards the left, and only a few bas-reliefs extend from the right into the left lobe, where they also terminate abruptly within the collapsed, hæmorrhagic tissue.

Gall Bladder: Is filled with light brown fluid bile.

Pancreas: Weighs 140 grm. and measures 17cm. long. It is rounded and flabby and dark in colour. On section, normal markings are indistinct.

Spleen: Weighs 240 grm. The surface is smooth and dark red in colour. The cut surface is dark red, and flabby and friable; the normal markings are indistinct.

Lymph Nodes: Mesenteric and retroperitoneal glands are enlarged and dark bluish in colour. They are palpable glands in the epitroclear, axillary and inguinal regions.

Kidneys. Right: The organ is of usual size and shape, but appears darker than normal. The capsule strips easily and the surface is smooth. The cut edges bulge. The differentiation between the cortex and medulla is poor. The pelvis is distended and contains large amount of dark clotted blood. The left kidney is similar in all respects to the right.

The ureters are distended and also filled with clotted blood, completely obliterating the lumen. The bladder contains bloody fluid.

HISTOLOGY

Liver: In sections it is quite easy to differentiate between the diffuse, hæmorrhagic areas and the swollen, paler, portions. The hæmorrhagic areas show complete collapse and obliteration of the liver tissue. Lobular arrangement can only be determined by the markedly dilated central veins and the peripheral, interlobular structures. The whole lobule is replaced by red blood cells, blood and bile (?) pigment, nuclear remains and indefinite fibrils. This hæmorrhagic necrosis

occupies the entire centre of the lobule and extends a variable distance to the periphery. As one approaches the interlobular spaces an infiltration by lymphoid and plasma cells becomes prominent and follows, more or less definitely, the course of the interlobular structures. Within these lymphoid cell infiltrations bile ducts are prominently displayed. The vessels of the interlobular tissue are dilated, and their perivascular spaces show similar cell infiltration. The portal bile ducts appear intact.

The picture of the swollen pale areas is as follows:

Around the central vein which is markedly dilated occurs irregular streaky necrosis which leads to destruction of the liver cells, leaving only bloodvessels and a fibrillar reticulum. These necroses are generally pale, and what blood appears in them is evidently still within vessels. They extend in streaks from the central vein to the interlobular spaces where they meet similar periportal, necrotic areas containing cellular remains. These periportal necroses show occasionally some lymphoid cell infiltration, but this, in this instance, is limited and frequently quite absent, and there is not any display of bile ducts within them. Between these inter-communicating central and peripheral streaks and necroses rest bands and areas of liver cells, occasionally still in columns and occasionally dislocated. These are generally widely separated by œdema and dilated, but not engorged, sinusoids which occasionally show fading red blood cells. The liver cells themselves are swollen, œdematous, often multinucleated, again atrophic and necrotic, a condition which seems to add to the gradually increasing separation of these cells. There is remarkable absence of fat, either in the form of intercellular infiltration or in the form of fatty cell disorganization.

It is interesting to note that the liver cells, although swollen and œdematous, do not show the general features of parenchymatous degeneration and necrosis, but rather a cytolysis incident to œdematous swelling and solution of cells, which reminds one much of the pictures seen in the cytolytic necrosis of liver cells in advanced venous stasis, fully described by

Oertel (*Archives of Int. Med.*, 1910, vi, 293, and *Berliner Klin. Wochenschrift*, 1912, xli, 2019), and Symmers (*Jour Exp. Med.*, vol. ix, 1907).

To recapitulate, then: The flat, red areas mostly conspicuous in the left lobe of the liver correspond to hæmorrhagic necroses with marked lymphoid cell infiltration from the interlobular periphery; the pale areas, constituting most of the right lobe of the liver, in which the parenchyma appears in relief, consist of inter-communicating central and peripheral, pale, necroses which surround swollen and disorganizing liver columns. In these, hæmorrhages are almost absent, and portal, lymphoid infiltration is also much less marked.

A consideration of these findings in the liver points at first to a similarity with acute yellow atrophy and toxic lesions produced by certain poisons: central and peripheral necroses in lobules with swelling of the remaining liver cells, collapse of liver tissue leading to extensive hæmorrhages and gradually increasing lymphoid cell infiltration carrying many bile ducts from the interlobular septa—are changes similar to those in early and later stages of acute yellow atrophy. Closer investigation, however, shows many points of characteristic difference which stamp the lesion essentially different in genesis and histological features.

There does not seem much doubt that the paler portions represent earlier stages of this process: in them the necrosis is limited, bands of liver cells and lobular arrangement are still preserved, hæmorrhages have not yet occurred, and perilobular lymphoid cell infiltration is absent or very limited.

These, apparently earlier, lesions display, as will be seen from the foregoing histological description, striking points of difference from those of acute yellow atrophy:

1. Cell death is not represented by coagulation necrosis which follows in the track of marked parenchymatous degeneration (characteristic of toxins primarily attacking parenchyma cells), but seems to be mainly due to œdematous swelling and solution of cells. Thus there remains even in necrosed areas a plain fibrillar reticulum, and the cells at the periphery of

these necroses are, although swollen and separated by œdema, unusually well preserved in protoplasm and nuclei, a condition which almost immediately attracts attention and sharply accentuates the necrotic areas from the surrounding liver cells.

2. Remarkable absence of fat in the necroses or even at their periphery. Herein lies a most striking point of difference between yellow atrophy, certain other parenchyma poisons, such as phosphorus, nutritive disturbances, and this case.

Intimately connected with, and probably dependent upon, these two points is:

3. The general absence of bile stasis, bile thrombi, bile pigmentation and cholangitis in the early stages, and the presence of only limited bile precipitation even in the older hæmorrhagic zones.

4. The tremendous amount of interstitial œdema and widening of capillaries which, as far as can be determined, represents the earliest change, and seems to inaugurate the cytolytic necrosis which follows closely the vascular portal distribution.

If we take these points into consideration, we note them not only as points of difference between this lesion and acute yellow atrophy or other toxic disintegrations, but more especially as throwing light on the genesis of this disease and the toxic affinity of trinitrotoluene.

For from these findings it appears probable that trinitrotoluene is essentially and primarily a vascular poison (endothelial toxin) which injures the capillary cells and lymphatics and thus leads to massive œdema, which in turn is followed by cytolitic necrosis following in the paths of this circulatory disturbance. The process leads sooner or later to collapse of liver lobules, extensive hæmorrhagic displacement, and later, as in other toxic liver destructions, to inflammatory interlobular cell infiltrations.

Whether this condition, which is acutely and subacutely displayed in this case, may also follow a more chronic course in which the anatomical expression more closely resembles

subacute atrophies and liver cirrhosis, seems possible, but must be determined by future anatomical observations.

Spleen: There is a tremendous amount of blood and blood pigment in the pulp, with loss of pulp tissue. The Malpighian corpuscles are relatively prominent. The whole organ is swollen and œdematous, and the sinuses are engorged with blood and pigmented cells.

Intestine: Sections of hæmorrhagic areas show marked œdematous swelling extending throughout all the coats, more especially in the submucosa. In it the bloodvessels are filled with numerous thrombi which, together with engorgement of the capillaries and free blood, give it an infracted appearance. The mucosa overlying these areas is necrotic and shows some cell infiltration, but the muscular and peritoneal layers are intact. Enlarged lymph gland from adjoining mesentery shows œdematous swelling, with marked dilatation and catarrh of the lymph sinuses.

Kidney: The whole kidney substance shows marked œdema and swelling which is especially pronounced in the interstitial tissues. The glomeruli are prominent and the capillary tufts engorged with blood, almost completely filling the capsule. In others the capillary loops appear fused, and the tuft plump and œdematous. The epithelium of the convoluted tubules is everywhere swollen and granular and in many places complete necrosis has occurred, leaving necrotic clumps in the lumen of these tubules. These changes are more or less limited to the convoluted tubules, while Henle's loops and collecting tubules show generally well preserved epithelium. The œdematous interlobular spaces show pinkish, widely separated fibrillæ and remnants of red blood cells, many of which are seen only in outline. In places the intertubular capillaries are engorged with blood.

The histological picture in the kidney seems to indicate that the cells of the convoluted tubules are at least equally involved with the vascular injury, for there the changes are quite characteristically those of parenchymatous degeneration and coagulation necrosis, thus differing from the parenchy-

matous disintegration in the liver. Whether this difference is due to a selective activity of the poison upon the cells of the convoluted tubules, or to the excretory activity of these cells, which would bring them into more direct contact with the poison or its products, as the result of its interference with body metabolism, must be left at present an open question.

EXPLANATION OF PLATES

Fig. 1. Section of liver : low power. Early central and peripheral streaky cytolysis, leaving hazy reticulum. Lobular intercolumnar œdema and swelling of liver cells, without parenchymatous or fat degeneration.

Fig. 2. Same under higher power. Note especially sharp line of demarcation between necrosis and intact liver cells, widely separated by œdema and capillary dilatation.

Fig. 3. Section of kidney. Note parenchymatous degeneration and coagulation necrosis in epithelium of convoluted tubules. Marked interlobular œdema. Plump, engorged and œdematous glomeruli, Henle's loops intact.
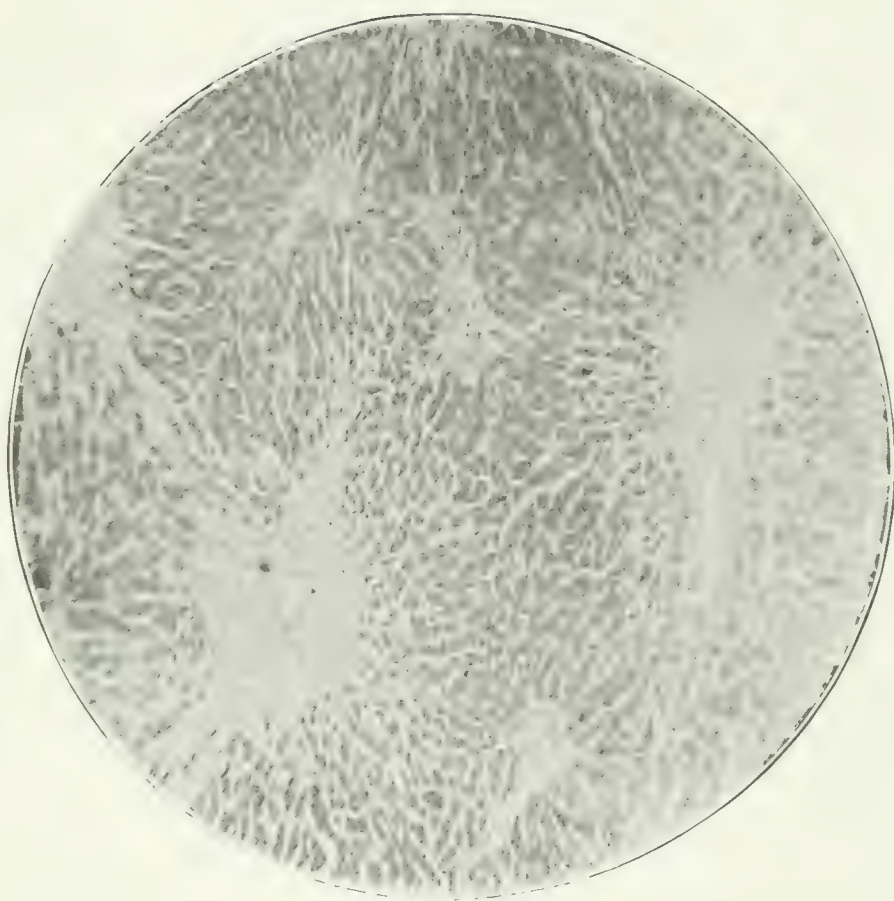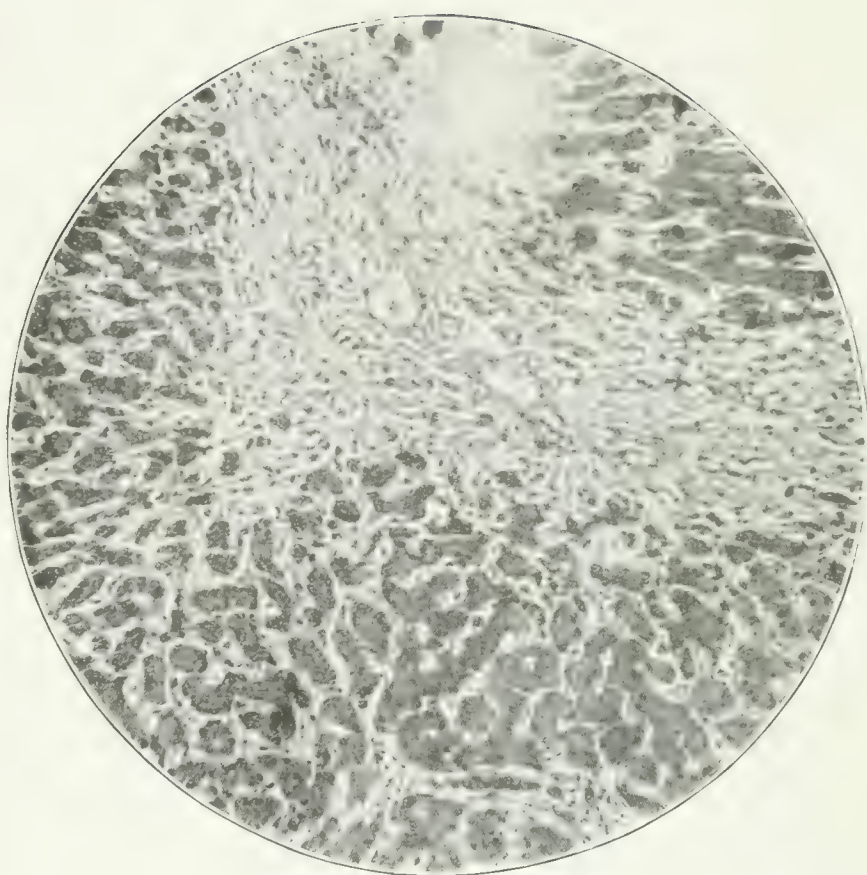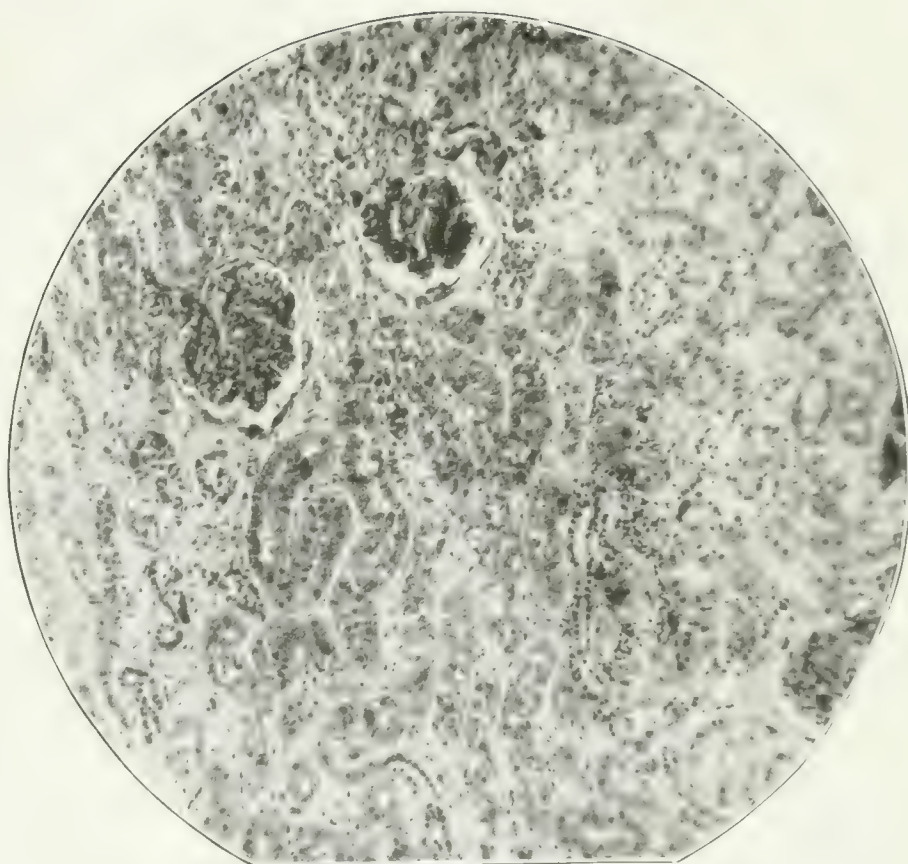
Fig. 1

Fig. 2

Fig. 3